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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

CADENCE PHARMACEUTICALS, INC. and SCR PHARMATOP,

Plaintiffs,

v.

FRESENIUS KABI USA, LLC,

Defendant.

CASE NO. **'13CV0139 LAB MDD**

COMPLAINT FOR PATENT INFRINGEMENT

COMPLAINT

Plaintiffs Cadence Pharmaceuticals, Inc. and SCR Pharmatop (collectively, "Plaintiffs") for their Complaint against defendant Fresenius Kabi USA, LLC ("Fresenius"), allege as follows:

PARTIES

1. Plaintiff Cadence Pharmaceuticals, Inc. ("Cadence") is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 12481 High Bluff Drive, Suite 200, San Diego, California, 92130. As set forth herein, Cadence is the exclusive licensee of the Patents-in-Suit.

2. Plaintiff SCR Pharmatop ("Pharmatop") is a civil law partnership organized and existing under the laws of France, having its headquarters at 10, Square St. Florentin, 78150 Le Chesnay, France. As set forth herein, Pharmatop is the assignee of the Patents-in-Suit.

3. Upon information and belief, defendant Fresenius is a limited liability company organized and existing under the laws of Delaware, having a principal place of business at 1501 East Woodfield Road, Suite 300 East, Schaumburg, Illinois, 60173. Upon information and belief, Fresenius is in the business of manufacturing, distributing, and selling pharmaceutical products throughout the United States, including in this judicial district.

NATURE OF THE ACTION

4. This is a civil action for infringement of United States Patent No. 6,028,222 and U.S. Patent No. 6,992,218 (collectively, the "Patents-in-Suit"). This action is based upon the Patent Laws of the United States, 35 U.S.C. § 100 e*t seq*.

JURISDICTION AND VENUE

5. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

6. This Court has personal jurisdiction over Fresenius because, *inter alia*, Fresenius has committed, or aided, abetted, actively induced, contributed to, or

participated in the commission of a tortious act of patent infringement that has led to foreseeable harm and injury to Cadence, a company with its principal place of business in this forum. This Court has personal jurisdiction over Fresenius for the additional reasons set forth below and for other reasons that will be presented to the Court if such jurisdiction is challenged.

7. This Court has personal jurisdiction over Fresenius because, *inter alia*, Fresenius has purposefully availed itself of the rights and benefits of California law by engaging in systematic and continuous contacts with California.

8. Upon information and belief, Fresenius regularly and continuously transacts business within the State of California, including by selling pharmaceutical products in California. Upon information and belief, Fresenius derives substantial revenue from the sale of those products in California and has availed itself of the privilege of conducting business within the State of California.

9. Venue is proper in this Court pursuant to 28 U.S.C. § 1391 and 28 U.S.C. § 1400(b).

THE PATENTS-IN-SUIT

10. United States Patent No. 6,028,222 ("the '222 patent"), titled "Stable Liquid Paracetamol Compositions, and Method for Preparing the Same," was duly and legally issued by the United States Patent and Trademark Office ("PTO") on February 22, 2000, to Pharmatop, the assignee of the named inventors. Pharmatop has been, and continues to be, the sole assignee of the '222 patent.

11. Pharmatop granted an exclusive license to the '222 patent to Bristol-Myers Squibb Company ("BMS"), with a right to sublicense. BMS in turn granted Cadence an exclusive sublicense, exclusive even to itself, to the '222 patent with regard to all rights pertinent to this action. A true and correct copy of the '222 patent is attached as Exhibit A.

12. United States Patent No. 6,992,218 ("the '218 patent"), titled "Method for Obtaining Aqueous Formulations of Oxidation-Sensitive Active Principles," was duly

and legally issued by the PTO on January 31, 2006, to Pharmatop, the assignee of the named inventors. Pharmatop has been, and continues to be, the sole assignee of the '218 patent.

13. Pharmatop granted an exclusive license to the '218 patent to BMS, with a right to sublicense. BMS in turn granted Cadence an exclusive sublicense, exclusive even to itself, to the '218 patent with regard to all rights pertinent to this action. A true and correct copy of the '218 patent is attached as Exhibit B.

OFIRMEV®

14. Cadence holds approved New Drug Application ("NDA") No. 022450 for OFIRMEV®, the first and only intravenous (IV) formulation of acetaminophen available in the United States. OFIRMEV® was approved by the Food and Drug Administration (the "FDA") on November 2, 2010. OFIRMEV® is indicated for the treatment of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever.

15. The publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") identifies drug products approved on the basis of safety and effectiveness by the FDA under the Federal Food, Drug, and Cosmetic Act. Pursuant to 21 U.S.C. § 355(b)(1) and attendant FDA regulations, the '222 patent and the '218 patent were listed in the Orange Book with respect to OFIRMEV®.

FRESENIUS'S INFRINGEMENT OF THE PATENTS-IN-SUIT

16. Upon information and belief, Fresenius submitted New Drug Application ("NDA") No. 20-4767 to the FDA, under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(b)), seeking approval to engage in the commercial manufacture, use, sale or offer for sale, and/or importation of Acetaminophen Injection, 10 mg/mL, 100 mL vials ("Fresenius's Generic Product"), as a generic version of the OFIRMEV® product, prior to the expiration of the Patents-in-Suit.

17. By a letter dated December 5, 2012 (the "Fresenius Letter"), Fresenius stated that it had submitted NDA No. 20-4767 seeking approval to engage in the

commercial manufacture, use, sale or offer for sale, and/or importation of Fresenius's Generic Product prior to the expiration of the Patents-in-Suit.

18. The Fresenius Letter also stated that NDA No. 20-4767 contains a "Paragraph IV certification" that alleges the '222 patent and '218 patent are invalid, unenforceable, and that Fresenius's Generic Product purportedly will not infringe any valid claim of the '222 patent and the '218 patent.

19. Upon information and belief, Fresenius has represented to the FDA that Fresenius's Generic Product will have the same active ingredient as OFIRMEV®, have the same route of administration, dosage form, and strength as OFIRMEV®, and is bioequivalent to OFIRMEV®.

20. Fresenius's submission of NDA No. 20-4767 to the FDA, including its section 355(b)(2)(A)(iv) allegations, constitutes infringement of the Patents-in-Suit under 35 USC § 271(e)(2)(A). Moreover, in the event that Fresenius commercially manufactures, imports, uses, offers for sale, or sells Fresenius's Generic Product or induces or contributes to such conduct, said actions would constitute infringement of the Patents-in-Suit under 35 USC § 271(a), (b) and/or (c).

21. Fresenius was aware of the Patents-in-Suit prior to filing NDA No. 20-4767, and its actions render this an exceptional case under 35 U.S.C. § 285.

22. The acts of infringement by the Fresenius set forth above will cause Plaintiffs irreparable harm for which they have no adequate remedy at law, and will continue unless enjoined by this Court.

COUNT I

(Infringement of the '222 Patent by Fresenius)

23. Plaintiffs incorporate each of the preceding paragraphs 1 to 22 as if fully set forth herein.

24. Fresenius's submission of NDA No. 20-4767, including its § 355(b)(2)(A)(iv) allegations, constitutes infringement of the '222 patent pursuant to 35 U.S.C. § 271(e)(2) by Fresenius.

25. On information and belief, upon FDA approval of NDA No. 20-4767, Fresenius will infringe the '222 patent by making, using, offering to sell, or selling Fresenius's Generic Product in the United States and/or importing Fresenius's Generic Product into the United States, and by actively inducing and/or contributing to infringement by others, in violation of 35 U.S.C. § 271(a), (b) and/or (c).

26. Upon information and belief, Fresenius had actual and constructive knowledge of the '222 patent prior to filing NDA No. 20-4767 and acted without a reasonable basis for a good faith belief that it would not be liable for infringing the '222 patent.

COUNT II

(Declaratory Judgment of Infringement of the '222 Patent by Fresenius)

27. Plaintiffs incorporate each of the preceding paragraphs 1 to 22 as if fully set forth herein.

28. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

29. Plaintiffs are further entitled to a declaration that, if Fresenius, prior to patent expiry, commercially manufactures, uses, offers for sale, or sells Fresenius's Generic Product within the United States, imports Fresenius's Generic Product into the United States, or induces or contributes to such conduct, Fresenius would infringe the '222 patent under 35 U.S.C. § 271(a), (b) and/or (c).

30. Plaintiffs will be irreparably harmed by Fresenius's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

COUNT III

(Infringement of the '218 Patent by Fresenius)

31. Plaintiffs incorporate each of the preceding paragraphs 1 to 22 as if fully set forth herein.

32. Fresenius's submission of NDA No. 20-4767, including its section 355(b)(2)(A)(iv) allegations, constitutes infringement of the '218 patent pursuant to 35 U.S.C. § 271(e)(2) by Fresenius.

33. On information and belief, upon FDA approval of NDA No. 20-4767, Fresenius will infringe the '218 patent by making, using, offering to sell, or selling Fresenius's Generic Product in the United States and/or importing Fresenius's Generic Product into the United States, and by actively inducing and/or contributing to infringement by others, in violation of 35 U.S.C. § 271(a), (b) and/or (c).

34. Upon information and belief, Fresenius had actual and constructive knowledge of the '218 patent prior to filing NDA No. 20-4767 and acted without a reasonable basis for a good faith belief that it would not be liable for infringing the '218 patent.

COUNT IV

(Declaratory Judgment of Infringement of the '218 Patent by Fresenius)

35. Plaintiffs incorporate each of the preceding paragraphs 1 to 22 as if fully set forth herein.

36. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

37. Plaintiffs are further entitled to a declaration that, if Fresenius, prior to patent expiry, commercially manufactures, uses, offers for sale, or sells Fresenius's Generic Product within the United States, imports Fresenius's Generic Product into the United States, or induces or contributes to such conduct, Fresenius would infringe the '218 patent under 35 U.S.C. § 271(a), (b) and/or (c).

38. Plaintiffs will be irreparably harmed by Fresenius's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A judgment that Fresenius infringed each of the Patents-In-Suit;

B. An order issued pursuant to 35 U.S.C. § 271(e)(4) that the effective date of any approval of Fresenius's NDA No. 20-4767 shall not be earlier than the expiration dates of the Patents-in-Suit, including any extensions and/or additional periods of exclusivity to which Plaintiffs are or become entitled;

C. A preliminary and permanent injunction restraining and enjoining Fresenius and its officers, agents, attorneys and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer to sell or sale within the United States, or importation into the United States of any of Fresenius's Generic Product until the expiration of the Patents-in-Suit, including any extensions and/or additional periods of exclusivity to which Plaintiffs are or become entitled;

D. That Plaintiffs be awarded monetary relief if Fresenius commercially manufactures, uses, offers for sale, or sells its generic version of Cadence's OFIRMEV® brand product, or any other product that infringes or induces or contributes to the infringement of the Patents-in-Suit, within the United States before the latest expiration date of any of the Patents-In-Suit, including any extensions and/or additional periods of exclusivity to which Plaintiffs are or become entitled;

E. A declaration that this is an exceptional case and an award of attorneys' fees pursuant to 35 U.S.C. § 285;

F. An award of costs and expenses in this action; and

G. Such other and further relief as the Court may deem just and proper.

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Dated: January 17, 2013

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EXHIBIT A

US006028222A

United States Patent [19]

Dietlin et al.

[11] **Patent Number: 6,028,222**

[45] **Date of Patent: Feb. 22, 2000**

[54] **STABLE LIQUID PARACETAMOL COMPOSITIONS, AND METHOD FOR PREPARING SAME**

[75] Inventors: **Francois Dietlin**, Le Pecq; **Daniele Fredj**, Gif-sur-Yvette, both of France

[73] Assignee: **SCR Pharmatop**, France

[21] Appl. No.: **09/051,246**

[22] PCT Filed: **Aug. 5, 1997**

[86] PCT No.: **PCT/FR97/01452**

§ 371 Date: **Jun. 5, 1998**

§ 102(e) Date: **Jun. 5, 1998**

[87] PCT Pub. No.: **WO98/05314**

PCT Pub. Date: **Feb. 12, 1998**

[30] **Foreign Application Priority Data**

Aug. 5, 1996 [FR] France 96 09858

[51] **Int. Cl.**[7] **C07C 209/90**

[52] **U.S. Cl.** **564/4**; 514/617; 564/2; 564/5; 564/6; 564/7; 564/223

[58] **Field of Search** 564/4, 5, 6, 7, 564/2, 223; 514/617

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Attorney, Agent, or Firm—Bierman, Muserlian and Lucas

[57] **ABSTRACT**

Novel stable paracetamol compositions for use in therapeutic chemistry and specifically galenic pharmacy are disclosed. The compositions contain a solution of paracetamol in an aqueous solvent combined with a buffer having a pH of 4 to 8, and a free radical capturing agent. A water-insoluble inert gas is carefully bubbled through the aqueous solvent to remove oxygen from the medium. Said compositions may also be combined with a centrally or peripherally acting analgesic agent, and are provided as injectable compositions for relieving pain.

28 Claims, No Drawings

STABLE LIQUID PARACETAMOL COMPOSITIONS, AND METHOD FOR PREPARING SAME

This application is a 371 of PCT/FR97/01452, filed Aug. 5, 1997.

FIELD OF THE INVENTION

The present invention relates to novel stable, liquid, analgesic formulations, containing paracetamol as main active ingredient, either in combination or not, with an analgesic derivative.

DISCUSSION OF THE PRIOR ART

It has been known for many years and notably from a paper of FAIRBROTHER J. E. entitled: Acetaminophen, published in Analytical Profiles of Drug Substances (1974), volume 3, pp. 1–109, that paracetamol in the presence of moisture, and all the more in aqueous solution, may be hydrolysed to yield p-aminophenol, which compound may itself be broken down into quinone-imine. The rate of decomposition of paracetamol is enhanced as the temperature is increased and upon exposure to light.

In addition, the instability of paracetamol in aqueous solution as a function of the solution's pH has been extensively described. Thus, according to a paper entitled "Stability of aqueous solution of N-acetyl-p-aminophenol" (KOSHY K. T. and LACH J. I. J. *Pharm. Sci.,* 50 (1961), pp. 113–118), paracetamol in aqueous solution is unstable, a fact which primarily correlates with hydrolysis both in acidic and basic environment. This breakdown process is minimal at a pH close to 6, the half-life of the product thus degraded namely being as high as 21.8 years at 25° C.

According to Arrhenium law and knowing the specific reaction constant as determined by these authors, the time needed to observe a 5% decrease in paracetamol concentration of an aqueous solution stored at 25° C. at the optimal pH as been predicted to be 19 months. Besides hydrolysis, the paracetamol molecule separately undergoes another kind of decomposition that involves formation of a quinone-imine that may readily polymerize with generation of nitrogen-containing polymers.

These polymers and in particular those stemming from N-acetyl-p-benzoquinone-imine have been further described as being the toxic metabolite of paracetamol, which is endowed notably with cytotoxic and hemolytic effect. The decomposition of this metabolite in aqueous medium is still more complex and gives rise to p-benzoquinone and hydroquinone (D. DAHLIN, J. Med. Chem., 25 (1982), 885–886).

In the current state of the art and in view of the quality control requirements specific to pharmaceutical practice regulations, the stability of paracetamol in aqueous solutions is thus insufficient and does not allow the formulation of liquid pharmaceutical compositions for injection. As a result, the successful preparation of liquid pharmaceutical formulations for parenteral administration, based on paracetamol, has not been achieved.

A number of trials has been undertaken to slow down the decomposition of paracetamol in aqueous solution. Thus, in a paper entitled: Stabilization by ethylenediamine tetraacetic acid of amide and other groups in drug compound, (FOGG Q. G. and SUMMAN, A. M., *J. Clin. Pharm. Ther.,* 17: (1992), 107–109), it is stated that a 0.1% aqueous solution of paracetamol has a p-aminophen content resulting from

hydrolysis of paracetamol, approximating 19,8% of the initial concentration of paracetamol, as observed after storage in the dark during 120 days. Addition of EDTA at a rate de 0.0075% brings down the decomposition rate to 7%. On the other hand, distilling an alkaline solution of paracetamol results in an ammonia concentration of 14%, in presence or not of 1000 ppm of ascorbic acid. Owing to its properties, ascorbic acid is indeed quite adapted to such stabilization. However, upon exposure to bright light, a paracetamol solution containing 1000 ppm of ascorbic acid does after all generate ammonia with a yield of 98%. In contrast, addition of EDTA (0.0075%) to such a solution cuts down decomposition rate, with an ammonia yield not higher than 14%.

Despite of such efforts, it has not been possible to prepare aqueous liquid solutions of paracetamol. In particular solutions for injection, having a guaranteed stability.

SUMMARY OF THE INVENTION

The present invention is aimed at solving the above stated problem in an appropriate manner. It is directed to stable pharmaceutical compositions of paracetamol in an aqueous solvent having added thereto a free radical antagonist. The aqueous solvent may be water or else aqueous mixtures containing water and a polyhydric compound such as polyethylene-glycol (PEG) 300, 400, 1000, 1540, 4000 or 8000, propylene glycol or tetraglycol. A water-soluble alcanol such as for example ethanol may also be used.

DETAILED DESCRIPTION OF THE INVENTION

Stability of the aqueous solutions mentioned above does not solely depend on the choice of a given carrier. It also depends on other variables, such as careful adjustment of pH, removal of oxygen dissolved in the carrier and addition of a free radical antagonist or a free radical scavenger.

Removal of dissolved oxygen is readily accomplished by bubbling an inert gas and preferably by bubbling nitrogen.

The appropriate free radical antagonist is chosen among the derivatives of ascorbic acid, those derivatives bearing at least a thiol functional group and straight chain or cyclic polyhydric compounds.

Preferred ascorbic acid derivatives are D- or L-ascorbic acid, an alkali metal ascorbate, an alkaline earth metal ascorbate or even still an aqueous medium-soluble ascorbic acid ester.

Free radical scavengers, bearing a thiol functional group may be an organic compound substituted by one or more thiol functional groups, of the aliphatic series such as cystein, acetylcystein, thioglycollic acid and salts thereof, thiolactic acid and salts thereof, dithlothreltol, reduced glutathion, thiourea, thioglycerol, methionine and mercaptoethane sulfonic acid.

The polyol used as a free radical scavenger is preferably a straight chain or a cyclic, polyhydroxy alcohol such as mannitol, sorbitol, inositol, isosorbide, glycerol, glucose and propylene-glycols.

Among free radical scavengers required pour stabilizing paracetamol, the ascorbic acid derivative currently preferred is sodium ascorbate. Preferred thiol functional group substituted derivatives are cystein, reduced-slate glutathion, N-acetylcystein and mercaptoethane sulfonic acid.

It may appear as convenient to combine several free radical scavengers as far as they are water-soluble and mutually compatible. Especially convenient free radical scavengers are mannitol, glucose, sorbitol or even glycerol. These may be readily combined.

It may appear as convenient to add to the preparation one or a number of complexing agents to improve stability of the molecule since the active ingredient is sensitive to the presence of trace metals that eventually speed up its decay.

Complexing agents are exemplified by nitrilotriacetic acid, ethylene diamino tetraacetic acid, ethylene diamino, N, N'-diacetic-N, N'-dipropionic acid, ethylene diamino tetraphosphonic acid, 2,2'-(ethylene diamino)dibutyric acid, or ethylene-glycol bis(diaminoethyl ether) N,N,N',N'-tetraacetic acid and sodium or calcium salts thereof.

The complexing agent also acts to complex bivalent ions (copper, zinc, calcium) that may be present and that have a negative influence of the aging of the formulation throughout storage.

The gas that is bubbled into the solution to drive out oxygen, may be nitrogen or carbon dioxide or still an inert gas. Nitrogen is favoured.

Isotonicity of the preparation may be achieved by adding an appropriate quantity of sodium chloride, glucose, levulose or postassium chloride, or calcium chloride, or calcium gluconoglucoheptonate, or mixtures thereof. The preferred isotonizing agent is sodium chloride.

The buffer used is a buffer compatible with parenteral administration in humans, the pH of which may be adjusted between 4 and 8. Preferred buffers are based on alkali metal ou alkaline earth metal acetates or phosphates. A more preferred buffer is sodium acetate/hydrogene phosphate adjusted to the required pH with hydrochloric acid or sodium hydroxide. The concentration of such a buffer may be comprised betwenn 0.1 and 10 mg/ml. The preferred concentration is confined in the range of 0.25 to 5 mg/ml.

On the other hand, preparations for injection have to be sterile and should lend themselves to heat treatment sterilization. It is known that in certain conditions, antioxidants such as glutathion are broken down]FIALAIRC A. et al., *J. Pharm. Biomed. Anal.*, vol. 10, No 6, pp. 457–460 (1992)]. The breakdown of reduced glutathion during heat treatment sterilization ranges from 40 to 77% depending on the selected temperature conditions. During such sterilization procedures, it is convenient to employ means capable of preserving the integrity of these antioxidants. Addition of complexing agents to aqueous solutions inhibits thermal decomposition of thiol derivatives, such as glutathion.

Liquid pharmaceutical compositions according to the invention are preferably compositions intended for injection. The paracetamol content of the solution may range from 2 mg/ml to 50 mg/ml in case of so called dilute solutions, i.e. that can be directly infused by intravenous route and from 60 mg/ml to 350 mg/ml where so-called concentrated solution are considered, i.e. either intended for direct injection by intravenous or intramuscular route, or intended to be diluted prior to slow infusion administration. The preferred concentrations are comprised between 5 and 20 mg/ml for dilute solutions and between 100 and 250 mg/ml for concentrated solutions.

Pharmaceutical compositions according to the invention may further contain another active ingredient that enhances the specific effect of paracetamol.

In particular, the pharmaceutical compositions according to the invention may contain a CNS-acting analgesic such as for example a morphinic analgesic.

The morphinic analgesic is selected among the morphinic derivatives of natural, semi-synthetic or synthetic origin and piperidine derivatives selected from the following list, which is no way intended to be exhaustive: buprenorphine, dramadol, codeine, dextromoramide, dextropropoxyphene, hydrocodone, hydromorphone, ketobemidone, levomethadone, levorphanol, meptazinol, methadone, morphine, nalbuphine, nicomorphine, dizocine, diamorphine, dihydrocodeine, dipipanone, methorphane, dextromethorphane.

Preferred morphinic derivatives are codeine sulfate or morphine hydrochloride.

The codeine or codeine derivative concentration, expressed in terms of codeine base, is comprised between 0.2% and 25% in relation to the paracetamol content. The preferred codeine derivative is codeine sulfate. The concentration thereof is set between 0.5 and 15% in relation to the paracetamol content.

The morphine or morphine derivative concentration, expressed in terms of morphine base, is comprised between 0.05 and 5% in relation to the paracetamol content. The preferred morphine derivative is morphine hydrochloride the concentration of which is preferably set between 0.5 and 15% in relation to paracetamol content.

The compositions according to the invention may further have added thereto an anti-inflammatory agent such as of the of AINS type and in particular a phenylacetic acid compound. Such agents are exemplified by ketoprofen, flurbiprofen, tiaprofenic acid, niflumic acid, diclofenac or naproxen.

Compositions according to the invention may in addition incorporate an antiemetic either a CNS-acting neuroleptic such as haloperidol or chlorpromazine or metopimazine or of the gastrokinetic-mediated type such as metochlopramide or domperidone or even a serotoninergic agent.

Compositions in accordance with the invention may further incorporate an anti-epileptic drug such as sodium valproate, clonazepam, carbamazepine or phenytoin.

It may also be possible to combine paracetamol with a corticosteroid such as for example prednisone, prednisolone, methyl prednisone, dexamethasone, betametasone or an ester thereof.

Paracetamol can further be combined with a tricyclic antidepressant such as amitriptiline, imipramine, clomipramine.

Anti-inflammatory agents may be included in concentrations ranging from 0.100 g to 0.500 g per 1000 ml of formulated product.

In Case of Concentrated Solutions

The water content expressed in percentage is preferably in excess of 5% of the total volume and more preferably comprised between 10 and 65%.

The quantity of propylene glycol formulated in percentage is preferably in excess of 5% and more preferably comprised between 20 and 50%.

The PEG used is preferably PEG 300, PEG 400, PEG 1000, PEG 1540 or PEG 4000. Concentrations used are comprised between 10 and 60% in weight. PEG 300 and PEG 400 are further preferred. Preferred concentrations range from 20 to 60%.

Ethanol concentrations range from 0 to 30% of total volume and preferably range from 0 to 20%.

Tetraglycol concentrations used do not exceed 15% to allow for maximal quantities that can daily be received by parenteral administration viz 0.7 ml/kg of body weight.

Glycerol concentration varies from 0.5 to 5% as a function of the viscosity of the medium suitable for use depending on the administrative route.

In Case of Dilute Solutions

The quantity of water used given in percentage is preferably in excess of 20% of the total volume and preferably is comprised between 25 and 100%.

The quantity of propylene-glycol employed given in percentage is preferably comprised between 0 and 10%.

The PEG used is preferably PEG 300, PEG 400, or PEG 4000 with PEG 4000 being most preferred. Preferred concentrations range from 0 to 10%. Tetraglycol concentrations used do not exceed 5%. In preference, they are comprised between 0 and 4%.

The ascorbic acid or ascorbic acid derivative concentration which is used is preferably more than 0.05 mg/ml and more desirably, comprised between 0.15 mg/ml and 5 mg/ml. Higher quantities may indeed be used, without exceeding the solubility limits. Higher ascorbic acid or ascorbic acid derivative concentration are administered to human beings for prophylactic or therapeutic purposes.

Thiol derivative concentration is comprised between 0.001% and 30% and more desirably, comprised between 0.005% and 0.5% for dilute solutions, and between 0.1% and 20% for concentrated solutions.

The pH of the solution is desirably adjusted taking into consideration the optimal stability of paracetamol in aqueous solution, i.e. at a pH around 6.0.

The thus prepared composition may be packaged in glass sealed vials, or in stoppered glass vials or in bottles made of a polymer material such as polyethylene, or in soft material bags made from polyethylene, polyvinyl chloride or polypropylene.

The composition may be sterilized by heat treatment, for example at 121° C. during 20 minutes or else by sterile filtration.

Currently preferred compositions in accordance with the invention have the following ingredients:

Concentrated solutions

Ingredient	Injection solution of paracetamol alone (per ml)	Injection solution of paracetamol associated to a morphinic compound (per ml) codeine	morphine
paracetamol	0.160 g	0.160 g	0.160 g
codein sulfate.$3H_2O$	—	0.0036 g	—
Morphine hydrochloride.$3H_2O$	—	—	0.00037
Propylene glycol	0.270 ml	0.270 ml	0.270 ml
PEG 400	0.360 ml	0.360 ml	0.360 ml
Sodium acetate	0.002 g	0.002 g	0.002 g
Reduced glutathion	0.002 g	0.002 g	0.002 g
Hydrochloric acid 1 N	q.s. pH 6.0*	q.s. pH 6.0*	q.s. pH 6.0*
Water for injection	q.s. 1000 ml	q.s. 1000 ml	q.s. 1000 ml
Nitrogen	q.s.f. bubbling	q.s.f. bubbling	q.s.f. bubbling

The pH specified above is the actual pH that has been measured by a pH-meter after obtaining a 5 fold dilution of the solution with distilled water. It will be noted that the apparent pH of the pure solution is different.

Using this solution composed of a solvent mixture constituted by 30% of propylene-glycol, by 40% of polyethylene-glycol 400 and by 30% of water (solution no 20), it is possible to dissolve about 200 mg/ml of paracetamol at 20° C. Choosing a concentration of 160 mg/ml allows one to be sure that no recristallization will occur, notably at low temperatures. In such situations, a volume of 6,25 ml of said solution contains 1000 mg of paracetamol.

Dilute solutions

Ingredient	Injection solution of paracetamol alone (per ml)	solution of paracetamol associated to codein (per ml) Such morphinic compound is codein	Such morphinic compound is morphine
paracetamol	0.0125 g	0.125 g	0.125 g
codein sulfate.$3H_2O$	—	0.00018 g	—
Morphine hydrochloride.$3H_2O$	—	—	0.000019 g
Mannitol	0.025 g	0.025 g	0.025 g
Sodium hydrogen phosphate dihydrate	0.0025 g	0.00025 g	000025 g
Sodium chloride	0.002 g	0.002 g	0002 g
Disodium ethylene diamino tetraacetate	0.0001 g	0.0001 g	0.0001 g
Hydrochloric acid or sodium hydroxide	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5
Water for injection	q.s.f. 1000 ml	q.s.f. 1000 ml	q.s.f. 1000 ml
Nitrogen	q.s.f. bubbling	q.s.f. bubbling	q.s.f. bubbling

The compositions according to the invention find therapeutic applications as pain relief drugs. For moderate pain, the solutions merely contain paracetamol. For acute pain, the solutions further contain a morphinic analgesic. Furthermore, the paracetamol solutions exert antipyretic activity.

The following examples are given by way of illustration and not by limitation.

EXAMPLE I

Determination of the Optimal Solvent Mixture

1.1 Concentrated solutions

Increasing quantities of paracetamol were introduced in the solvent mixtures. The dissolution rate of paracetamol increases with rise in temperature, so that the solubility tests in the individual media were run by heating the solvent mixture to 60° C. After dissolution was judged complete, the solutions were stored for 72 hours either at 25° C. or 4° C.

The solubility values are listed in the following table:

Test n°	Water (ml)	Propylene-glycol (ml)	PEG 400 (ml)	Ethanol	Tetraglycol (ml)	Solubility at +4° C. (mg/ml)	Solubility at +25° C. (mg/ml)
1	0.3	0.4	0.3	—	—	110	130
2	0.4	0.3	0.3	—	—	110	130
3	0.16	0.3	0.4	—	0.15	190	230
4	0.5	—	0.5	—	—	110	150
5	0.4	0.3	0.2	0.1	—	<110	120
6	0.5	0.3	0.1	0.1	—	<100	130
7	0.4	0.4	0.1	0.1	—	<100	150
8	0.5	0.3	0.2	—	—	<100	120
9	0.6	0.3	0.2	—	—	<100	<100
10	0.5	0.4	0.1	—	—	<100	<100
11	0.55	0.3	0.05	0.1	—	<100	<100
12	0.45	0.4	0.05	0.1	—	<100	120
13	0.65	0.3	0.05	—	—	<100	<100
14	0.55	0.3	0.05	—	—	<100	<100
15	0.4	0.4	0.2	—	—	<100	<150
16	0.45	0.45	0.1	—	—	<100	<100
17	0.4	0.2	0.4	—	—	160	200
18	0.5	0.2	0.3	—	—	160	160
19	0.5	0.1	0.3	—	—	100	190
20	0.3	0.3	0.4	—	—	190	200
21	0.3	0.3	0.35	—	0.15	160	210
22	0.25	0.25	0.35	—	0.15	170	220

The solubility values of the solvent mixtures do not increase in a consistent manner with increasing temperature. Solubility is not enhanced if ethanol is added.

In addition, due to oversaturation phenomena which are observed in such solutions, notably in media containing PEG, a delayed recristallization was noted subsequent to cooling. In these conditions, the solutions under study were kept for 14 days at 20° C., then there was added, to the solutions displaying no cristals following this time interval, a paracetamol germ cristal in order to elicit cristallization of potentially oversaturated solutions. Finally, it was found that solutions no 20 and no 3 have the highest solubility with respect to paracetamol, which threshold was comprised between 160 mg/ml and 170 mg/ml depending on temperature.

1.2 Dilute solutions

Paracetamol is quantities well exceeding the solubility threshold was introduced in the solvent mixtures previously warmed to 30° C. After stirring and cooling at 20° C., the solutions were filtered. The paracetamol content of these solutions was determined by reading the absorbance at 240 nm of a 1:200 dilution of the filtrate.

The results are recorded in the following tables.

Type of solution (unless otherwise stated, the main solvent is distilled water)	concentration of paracetamol (mg/50 ml)
Water	720
5% Glucose	710
4.82% levulose	730
7% mannitol	680
5% sorbital	685
0.9% sodium chloride	615
10% Calcium gluconoglucoheptonate	670
Lestradet's solution (5% glucose, 0.2% sodium chloride, 0.15% potassium chloride, 1.1% calcium gluconoglucoheptonate)	730
Ringer's solution (0.7% sodium chloride, 0.1% potassium chloride, 0.1% sodium chloride)	730
Ringer's solution-Phosphate (0.7% sodium chloride, 0.182% monopotassium phosphate, 0.182% calcium chloride)	710
Ringer's solution-acetate (0.7% sodium chloride, 0.131% potassium acetate 0.013% calcium chloride)	715
Urea 0.3 M	725
Type of solution (the following solutions were prepared in Ringer's solution)	
Pure Ringer's solution	735
4.0% PEG 4000 + 1.0% propylene-glycol + 0.5% ethanol	905
4.0% PEG 4000 + 1.0% propylene-glycol + 1.0% ethanol	905
4.0% PEG 4000 + 1.0% propylene-glycol + 2.0% ethanol	930
Type of solution (the following solutions were prepared in 0.9% sodium chloride solution)	
0.9% sodium chloride	615
+0.6% tetraglycol	640
+1.2% tetraglycol	680
+3.0% tetraglycol	720
1.0% PEG 4000	630
1.0% PEG 4000 + 0.6% tetraglycol	660
1.0% PEG 4000 + 1.2% tetraglycol	710
3.0% PEG 4000 + 2.0% tetraglycol	950

Paracetamol solubility is increased by the presence of PEG.

Solubilities of paracetamol in mixtures of PEG 4000 and 0.9% sodium chloride solutions were determined in distilled water, at concentrations ranging from 0 to 7%, as a function of temperature.

The results are given in the following table:

PEG 4000 concentration (%/vol.) in 0.9% sodium chloride solution	Solvent volume (ml) required to dissolve 1000 mg of paracetamol as a function of temperature				
	4° C.	17° C.	22° C.	30° C.	42° C.
0%	130	92	80	65	42
1%	99	78	67	63	47
2%	91	72	63	59	45
3%	80	64	56	54	41
4%	82	62	57	49	36
5%	79	59	51	46	34
7%	78	61	48	42	30

4.1 Concentrated solution

Ingredient	Quantity	
	Solution without nitrogen bubbling	solution subjected to nitrogen bubbling
Paracetamol	0.160 g	0.160 g
Propylene-glycol	0.270 ml	0.270 ml
PEG 400	0.360 ml	0.360 ml
Sodium hydroxide or HCl 1N	q.s. pH 6.0	q.s. pH 6.0
Nitrogen	none	q.s.f. purging and filling
Water for injection	q.s.f 1000 ml	q.s.f. 1000 ml

Solution 20 containing paracetamol in a quantity of 160 mg/ml, adjusted to pH 6.0 by sodium hydroxide or hydrochloric acid 1N, was either subjected or not subjected to nitrogen gas bubbling. Tightly stoppered and capped vials packed by dispensing 10 ml of such solutions under nitrogen atmosphere or air, were sterilized by autoclaving at 121° C. during 20 minutes. The percentage of secondary peaks was then measured by liquid chromatography with respect to the main peak of paracetamol, as well as was the pink color strength by reading the solution absorbance by absorption spectrophotometry at peak absorbance wavelength, that is 500 nm.

Results

Solution tested	Secondary peaks in % of main peak of paracetamol	absorbance of the solution at 500 nm
Autoclaved solution packed without nitrogen	0.054	0.08
Autoclaved solution packed under nitrogen	0.036	0.03

It is therefore seen that the difference in color of the solution packed under nitrogen is very striking.

In order to check if 0% and 1% PEG-paracetamol solutions remain clear under cold storage, the following solutions ere prepared:

Ingredient	Solution without PEG	Solution with PEG added
Paracetamol	1 g	1 g
PEG 4000	—	1 g
0.9% Sodium chloride solution in water for injection	q.s. 125 ml	q.s. 100 ml

After storage of these solutions at 4° C. during 10 days, none of the vials tested showed cristallization. Presence of PEG is therefore not mandatory if the solutions are to remain clear throughout the time interval studied.

EXAMPLE II

Tests Conducted for Characterizing Paracetamol Breakdown in Solution

2.1 Demonstrating paracetamol instability in solution

A paracetamol solution in water or in solution no 20 shows rapidly a pink color upon exposure to light or storage at high temperature. At 50° C., color development occurs in 2 weeks time. Appearance of such color tinge correlates with an increase in solution absorbance at a peak absorbance wavelength of 500 nm. According to the paper of Fairbrother mentioned above, exposure of paracetamol to moisture can result in hydrolysis with formation of para-aminophenol, followed by oxydation, with appearance of a pink color, typical of the production of quinoneimine.

2.2 Identifying the breakdown products of paracetamol

In aqueous or partially aqueous solutions, p-aminophenol is not detected during storage. Rapid production of colored products having a pink tinge is noted, the reaction rate being a function of temperature and light. In course of time, such derivatives are increasingly dark and evolutes to brown color.

All occurs as if, in contrast to what has been reported in the literature, the breakdown of paracetamol first involves an oxydative process followed by hydrolysis. According to this theory, paracetamol may react with an oxidant present in solution, for example oxygen dissolved in the aqueous layer. This mechanism may involve the production of free radicals resulting in molecular coupling, a fact that may account for the production of colored derivatives evoluting in color from pink to brown.

2.3 Tests for demonstrating inhibition of free radical production

A typical reaction involving the production of free radicals involves adding a 30% aqueous solution of hydrogen peroxide and a copper pentahydrate solution at a concentration of 62.5 mg/ml, to a 1.25% aqueous solution of paracetamol. In a matter of minutes, there develops a color reaction resulting in a color shift from yellow to dark brown. The color intensity observed decreases if free radical scavengers or glycerol are prior added to the paracetamol solution. Color intensity is a function of type of the type of free radical scavenger added, in the following decreasing order as judged by color intensity.

Paracetamol alone>paracetamol+N-acetylcystein>paracetamol+cystein>paracetamol+sorbitol>paracetamol+mannitol>paracetamol+glycerol.

EXAMPLE III

Stabilizing paracetamol solution by selecting the pH that allows maximal stability

3.1 Concentrated solution

Ingredient	Quantity
Paracetamol	0.160 g
Propylene-glycol	0.270 ml
PEG 400	0.360 ml
Sodium hydroxide 1N	pH 7.0–8.0–9.0–9.5–10.0 corresponding
or Hydrochloric acid 1N q.s.f.	to actual pH: pH 5.8–6.7–7.1–7.5–8.0–8.5
Nitrogen q.s.f.	purging and filling
Water for injection	q.s. 1000 ml

Solution 20 containing paracetamol in a concentration of 160 mg/ml was adjusted to different pH's: the apparent pH is given in comparison to actual pH (between parenthesis) after a 5 fold-dilution: 7,0 (5,8)-8,0 (8,7)-8,5 (7,1)-9,0 (97,5)-9,5 (8,0)-10.0 (8,5) using a sodium hydroxide or normal hydrochloric acid solution. Vials that had been filled under nitrogen atmosphere by dispensing 10 ml of such solutions, tightly stoppered and capped, were sterilized by autoclaving at 121° C. for 20 minutes, and then in every case exposed, either to a temperature of 105° C. in the dark for 72 hours, or to a radiation of an actinic light at 5000° K. and 25° C. during 264 hours.

Results

After autoclaving, only the solution adjusted to pH 10 shows a pink tinge. After storage at 105° C. for 72 hours, absorbance at 500 nm as well as the concentration of breakdown products of paracetamol were minimal in the pH range from 7,5 to 9,5. Upon storage in the presence of light, the color strength is enhanced as the pH is increased. Color development is extremely weak at pH 7,0 (actual pH 5,8). Neither the paracetamol content, nor the breakdown products are affected by pH.

3.2 Diluted solution

Ingredient	Quantity
Paracetamol	0.008 g
Sodium chloride	0.0067 g
Disodium phosphate dihydrate	0.0012 g
5% Citric acid q.s.f.	pH 5.0–6.0–7.0
Nitrogen q.s.f.	bubbling and filling
Water for injection	q.s.f. 1000 ml

The aqueous solution diluted and buffered having a paracetamol content of 8 mg/ml was adjusted to different pH values: pH 5,0–7,0 using a citric acid solution.

Vials that had been packed under nitrogen atmosphere by dispensing 10 ml of such solution, were tightly stoppered and capped, sterilized by autoclaving at 121° C. for 20 minutes, and then in every case exposed to 70° C. in the dark during 231 hours.

Results

Following autoclaving, only the solution adjusted to pH 7 shows a pink color. After storage, this same solution displays the brightest pink color. At pH 6,0 and 5,0 the solutions are faintly colored.

EXAMPLE IV

Stabilization of Paracetamol in Solution by Oxygen Removal Through Nitrogen Bubbling

4.2 Diluted solution

Solution Tested

	Quantity	
Ingredient	Solution without nitrogen bubbling	solution subjected to nitrogen bubbling
Paracetamol	0.008 g	0.008 g
Sodium chloride	0.008 g	0.008 g
Disodium phosphate dihydrate	000.1 g	0.001 q
5% Citric acid	q.s.f. pH 6.0	q.s.f. pH 6.0
Nitrogen	none	q.s.f. purging and filling
Water for injection	q.s.f. 1000 ml	q.s.f. 1000 ml

The diluted aqueous solution containing paracetamol is adjusted to pH 6,0 by means of a citric acid solution.

Vials that had been filled under a nitrogen atmosphere by dispensing 10 ml of such solutions, were tightly stoppered and capped and then stored inside an incubator at 98° C. for 15 hours.

The percentage of secondary peaks in relation to the main peak of paracetamol was measured by liquid chromatography, so was the pink color strength by reading the solution absorbance by absorbance spectrophotometry at a peak absorption wavelength, that is 500 nm.

Results

Solution tested	Secondary peaks in % of paracetamol main peak	Solution absorbance at 500 nm
Solution packed without nitrogen atmosphere	1.57	0.036
solution packed under nitrogen atmosphere	0.44	0.016

The pink color of the solution packed under nitrogen atmosphere is considerably tainter than that observed for the solution obtained after sterilization under nitrogen of the solution packed without nitrogen.

EXAMPLE V

Stabilizing Solutions of Paracetamol by Adding Free Radical Antagonists

5.1 Concentrated solution

Ingredient	Quantity
Paracetamol	0.160 g
Propylene-glycol	0.270 ml
PEG 400	0.360 ml
Hydrochloric acid 1N	pH 6.0
or NaOH 1N q.s.f.	

-continued

Ingredient	Quantity
Free radical scavenger (see quantitative results)	q.s.f. (see quantitative results)
Nitrogen q.s.f.	purging and filling
Water for injection	q.s.f 1000 ml

The solutions thus prepared are divided in 10 ml capacity vials, stoppered with a Bromobutyl stopper and capped with an aluminium cap. After autoclaving at 121° C. for 20 minutes, the vials were stored for 48 hours, either in the presence of actinic light at 5500° K. at room temperature or at 70° C. in the dark. The preparation was examined for any change in color.

Results

Free radical scavenger	Concentration	Appearance of the solution upon exposure to light Color intensity	Appearance of solution at 70° C. Color intensity
No scavenger	—	pink (+)	pink (++)
Sodium disulfite	0.295 mg/ml	colorless	colorless
Sodium ascorbate	1.0 mg/ml	yellow (+)	yellow (+)
Reduced glutathion	1 mg/ml	colorless	colorless
Reduced glutathion	8 mg/ml	colorless	colorless
Cystein hydrochloride	1 mg/ml	cloudy	cloudy
α-monothioglycerol	1 mg/ml	colorless	colorless
Dithiothreitol	1 mg/ml	colorless	colorless
Mannitol	50 mg/ml	colorless	colorless

5.2 Dilute solution

Solutions tested

Ingredient	Quantity Formulation A	Formulation B	Formulation C
Paracetamol	0.008 g	0.01 g	0.0125 g
Sodium chloride	0.008 g	0.008 g	0.00486 g
Disodium phosphate dihydrate or sodium acetate	0.001 g	0.001 g	0.00125 g
Hydrochloric acid	q.s. pH 6.0	q.s. pH 6.0	q.s pH 5.5
C.R.L.	q.s (see quantitative results)		
Nitrogen q.s.f.	purging and filling		
Water	q.s.f. 1000 ml		

The solutions thus prepared were divided in 10 ml, 100 ml or 80 ml capacity vials, stoppered with a Bromobutyl stopper and capped with an aluminium cap. The preparation was examined for any pink color development.

After autoclaving at 121° C. for 20 minutes, the vials were stored for 48 hours, either in the presence of actinic light at 5500° K. at room temperature or at 70° C. in the dark (formula A).

After autoclaving at 124° C. for 7 minutes, the vials were stored for 48 hours at room temperature in the dark (formulation B and C). The preparation was examined for any pink shift and the paracetamol as well as CRL were measured where a thiol derivative was used.

Results (CRL=free radical scavenger)

C.R.L used	Concentration	Solution appearance upon exposure to light color	strength	Solution appearance at 70° C. color	strength
No C.R.L.	—	pink	(+)	pink	(++)
Thiourea	0.5 mg/ml	colorless		colorless	
Dithiothreitol	1 mg/ml	colorless		colorless	
α-monothio-glycerol	1 mg/ml	colorless		colorless	
gluthathion	1 mg/ml	colorless		colorless	
Sodium	0.2 mg/ml	pink	(+)	pink	(+)
ascorbate	0.4 mg/ml	colorless		yellow	(+)
	0.6 mg/ml	pink	(+)	yellow	(+)
	1.0 mg/ml	colorless		yellow	(+)
Cystein	0.05 mg/ml	colorless		colorless	
hydrochloride	0.1 mg/ml	colorless		colorless	
	0.25 mg/ml	colorless		colorless	
	0.5 mg/ml	colorless		colorless	
	0.75 mg/ml	colorless		colorless	
	1 mg/ml	colorless		colorless	
	2 mg/ml	colorless		colorless	
	5 mg/ml	colorless		colorless	

C.R.L used	Concentration	Solution appearance color	strength	Dosages (in % of theoretical volume C.R.L.	paracetamol
Cystein hydrochloride monohydrate	0.2 mg/ml	colorless		80%	99.2%
Cystein hydrochloride monohydrate	0.5 mg/ml	colorless		95%	99.6%
N-acetylcystein	0.2 mg/ml	colorless		88%	99.2%
Mannitol	20 mg/ml	colorless			
Mannitol	40 mg/ml	colorless			
Mannitol	50 mg/ml	colorless			
Glucose	50 mg/ml	colorless			

EXAMPLE VI

Stabilization of Solutions of Paracetamol Containing a Morphinic Compound by Addition of a Free Radical Scavenger

6.1 Concentrated solution

Solutions tested

Ingredient	Quantity
Paracetamol	0.160 g
Codein phosphate	0.008 g
Propylene-glycol	0.270 ml
PEG 400	0.360 ml
Hydrochloric acid 1N q.s.	q.s. pH 6.0
Free radical scavenger	q.s. (see quantitative results)
Water for injection	q.s.f. 1000 ml

The solutions thus prepared were divided in 10 ml capacity vials, stoppered with a Bromobutyl stopper and capped with a removable aluminium cap. After autoclaving at 121° C. for 20 minutes, the vials were stored for 48 hours either under actinic light at 5500° K. at room temperature, or at 70° C. in the dark. The preparation was inspected for any change in color.

Results

Free radical scavenger	Concentration	Solution apperance upon exposure to light: color	strength	Solution apperance 70° C.: color	strength
No free radical scavenger	—	pink	(+)	pink	(++)
Sodium disulfite	0.295 mg/ml	yellow	(+)	yellow	(++)
Sodium ascorbate	1.0 mg/ml	yellow	(++)	yellow	(+++)
reduced glutathion	1 mg/ml	yellow	(+)	amber yellow	(+++)
	8 mg/ml	colorless		yellow	(++)
	16 mg/ml	colorless		yellow	(+)
Dithio-threitol	1 mg/ml	violet pink	(+++)	violet pink	(++++)
sodium hypo-phosphite	5 mg/ml	pink	(+)	pink	(++)

6.2 Dilute solutions

Solutions tested

Ingredient	Quantity
Paracetamol	0.008 g
Codein phosphate	0.0004 g
Sodium chloride	0.008 g
Disodium phosphate dihydrate	0.0015 g
Hydrochloric acid	q.s.f. pH 6.0
Free radical scavenger	q.s. (see results)
Nitrogen q.s.f.	purging and filling
Water for injection	q.s.f. 1000 ml

The solutions thus prepared were divided in 10 ml capacity vials, stoppered with a Bromobutyl stopper and capped with an aluminium cap. After autoclaving at 121° C. for 20 minutes, the vials were stored for 48 hours, either under actinic light at 5500° C. at room temperature, or at 70° C. in the dark. The preparation was examined for any change in color.

For the solution not containing any free radical scavenger and for the solution containing 0.5 mg/ml of cystein hydrochloride as free radical antagonist, paracetamol as well as codein are measured by high performance liquid chromatography, immediately after autoclaving, in comparison with identical solutions not subjected to autoclaving.

Appearence scoring of the solutions

Free radical scavenger	Concentration	Solution apperance upon exposure to light: color	strength	Solution apperance 70° C.: color	strength
No free radical scavenger	—	pink	(+)	pink	(+)
Sodium disulfite	0.295 mg/ml	colorless		colorless	
Dithio-threitol	0.5 mg/ml	colorless		colorless	

-continued

Free radical scavenger	Concentration	Solution apperance upon exposure to light: color	strength	Solution apperance 70° C.: color	strength
Monothio-glycerol	0.5 mg/ml	grey		grey	
Reduced glutathion	2.0 mg/ml	colorless		colorless	
N-acetylcystein	2.0 mg/ml	grey	(+)	grey	(+)
Cystein hydro-chloride	0.05 mg/ml	colorless		pink	(+)
	0.1 mg/ml	colorless		colorless	
	0.25 mg/ml	colorless		colorless	
	0.5 mg/ml	colorless		colorless	
	0.75 mg/ml	colorless		colorless	
	1.0 mg/ml	colorless		colorless	
	2.0 mg/ml	colorless		colorless	
	5.0 mg/ml	colorless		colorless	

Assay results of paracetamol and codein

Solution tested	Ingredient assayed	non sterilized solution	after sterilization
Solutions with no free radical scavenger added	paracetamol	0.0078 g/ml	0.0077 g/ml
	codein	0.00043 g/ml	0.00042 g/ml
Solution containing 0.5 mg/ml of cystein hydrochloride	paracetamol	0.0082 g/ml	0.0081 g/ml
	codein	0.00042 g/ml	0.00042 g/ml

There is noted the lack of color development one one hand and excellent preservation of the active ingredients after heat treatment sterilization on the other hand.

EXAMPLE VII

Biological Tolerance to the Preparation

7.1 Hematological tolerance

Tested solutions

Ingredient	Quantity
Paracetamol	0.160 g
Propylene-glycol	0.270 ml
PEC 400	0.360 ml
Nitrogen q.s.f.	purging and filling
Water for injection	q.s.f. 1000 ml

The solution pH was not adjusted. The apparent pH is 7.6, corresponding to an actual pH of 6.5.

Whole human blood is incubated with the solution under study, in equal proportions by volume. 2 ml were drawn at 10 minutes intervals and centrifuged for 5 minutes at 5000 rpm. 100 μl of the supernatant were diluted in 1 ml of distilled water. The absorbance of this solution was determined against a water blank at 540 nm, peak absorption wavelength of hemoglobin.

The study was run in comparison with a negative control (physiological saline) and a positive control (pure water for injection).

Results

The absorbances of the individual solutions after different incubation periods are provided in the following table.

Solution	TO	10 min	20 min	30 min	40 min	50 min	60 min
Water p.p.i	2.23	2.52	2.30	2.37	2.38	2.33	2.36
Physio-logical saline	0.04	0.05	0.05	0.05	0.04	0.05	0.04
Sol. Tested	0.09	0.19	0.27	0.25	0.24	0.24	0.25

7.2 Muscular tolerance

Solution tested

Ingredient	Quantity
Paracetamol	0.160 g
Propylene-glycol	0.270 ml
PEG 400	0.360 ml
Nitrogen q.s.f.	purging and filling
Water for injection	q.s.f. 1000 ml

The pH of this solution was not adjusted. Apparent pH is equal to 7,6.

Sprague-Dawley rats, weighing between 260 g and 450 g were anesthesized with an i.p. injection of ethyl carbamate (2 ml/kg of a 50% aqueous solution). The extensor digitorum longus muscle was dissected from the right or left hind leg, and placed in buffer medium having the following composition:

Ingredient	Quantity
Sodium chloride	6.8 g
Potassium chloride	0.4 g
Dextrose	1.0 g
Sodium bicarbonate	2.2 g
Phenol red (sodium salt)	0.005 g
Distilled water q.s.f.	1 liter
Hydrochloric acid 1N q.s.f.	pH 7.4

The muscle is transiently fixed to a board and maintained in position by tendons. The test product was injected in an amount of 15 μl by means of a 25 μl-capacity Hamilton seringe no 702. The muscle is then placed over a grit and immersed in the buffer solution kept at 37° C. with carbogen bubbling throughout the incubation period. At 30 minutes intervals, the muscles were introduced in a tube containing fresh buffer at 37° C. The procedure was repeated 4 times.

The buffer solution hence incubated is assayed for creatine kinase activity.

The study was run in parallel with:

muscle alone not subjected to injection (blank)

needle alone (introducing the needle without product injection)

physiological saline

Triton X-100 solution (negative controls)

solution 20

solution 20+paracetamol 160 mg/ml.

Creatine kinase was measured using a Hitachi 704 model analyzer in conjunction with a reagent kit sold under tradename high performance Enzyline CK NAC 10 (Biomerieux).

Results

The creatine kinase activity (IU/l) of the individual solutions after variable incubation periods are provided in the table given hereinafter:

Solution tested	30 min	60 min	90 min	120 min	Total
Muscle alone	23 ± 6	24 ± 12	15 ± 7	13 ± 5	75
Needle alone	35 ± 6	33 ± 10	20 ± 4	18 ± 7	106
Physiological saline	30 ± 6	10 ± 12	17 ± 6	23 ± 4	100
Triton-X	1802 ± 2114	1716 ± 978	155 ± 89	289 ± 251	14962
Solution 20 (excipients)	71 ± 24	89 ± 40	39 ± 27	62 ± 39	261
Solution 20 + paracetamol	141 ± 40	150 ± 60	68 ± 63	34 ± 24	393

No necrosis signs were recorded using the composition according to the invention as no significant difference between the results of test and excipient solutions was noted.

What is claimed is:

1. A stable, liquid formulation consisting essentially of acetaminophen dispersed in an aqueous medium containing a buffering agent and at least one member of the group consisting of a free radical scavenger and a radical antagonist.

2. The formulation of claim 1 wherein the aqueous medium has been deoxygenated by bubbling a water-insoluble inert gas.

3. The formulation of claim 1 wherein the aqueous medium is buffered at a pH of 4 to 8.

4. The formulation of claim 3 wherein the aqueous medium is buffered at a pH of 5.5 to 6.

5. The formulation of claim 1 containing a free radical antagonist selected from the group consisting of ascorbic acid ascorbic acid derivatives, organic compounds having at least one thiol and a alkyl polyhydroxylated and cycloalkyl polyhydroxylated compounds.

6. The formulation of claim **5** wherein the ascorbic acid derivatives ar selected from the group consisting of D-ascorbic acid, L-ascorbic acid, alkali metal ascorbates, alkaline earth metal ascorbates and water-soluble ascorbic acid esters.

7. The formulation of claim **5** wherein the organic compound having at least one thiol is aliphatic or cycloaliphatic.

8. The formulation of claim **1** containing a free radical scavenger containing at least one thiol is selected from the group consisting of thiolyglycolic acid, thiolacetic acid, dithiothreitol, reduced glutathion, thiourea, α-thioglycerol, cystein, acetlcystein and mercaptoethane sulfonic acid.

9. The formulation of claim **1** wherein the free radical scavenger is an aliphatic polyhydroxy alkanol of 2 to 10 carbon atoms.

10. The formulation of claim **9** wherein the polyhydroxy alkanol is a cyclic glucitol or a straight chain glucitol of 6 to 10 carbon atoms.

11. The formulation of claim **9** wherein the polyhydroxy alkanol is glycerol or propyleneglycol.

12. The formulation of claim **10** wherein the cyclic glucitol is selected from the group consisting of mannitol, sorbitol, inositol, glucose and levulose.

13. The formulation of claim **1** also containing at least one complexing agent.

14. The formulation of claim **1** wherein the acetaminophen has a concentration of 2 to 350 mg/ml.

15. The formulation of claim **14** wherein the concentration is 60 to 350 mg/ml.

16. The formulation of claim **14** diluted to a concentration of 2 to 50 mg/ml.

17. The formulation of claim **1** also containing an isotonizing agent in an amount to obtain isotonicity.

18. The formulation of claim **1** sterilized by heat treatment.

19. The formulation of claim **1** further containing an effective amount of an analgetic agent.

20. The formulation of claim **19** the analgetic agent is a morphine analgetic selected from the group consisting of natural morphines, semi-synthetic morphines, synthetic morphines, phenylpiperidines, nipecotic acid compounds, phenylcyclohexanol compounds and phenylazepine compounds.

21. The formulation of claim **20** having a concentration of acetaminophen is 0.05 to 5% by weight when morphine is present.

22. The formulation of claim **20** having an acetaminophen concentration of 0.2 to 2.5% by weight when codeine is present.

23. The formulation of claim **1** further containing an anti-inflammatory agent of the phenylacetic acid type.

24. The formulation of claim **23** wherein the anti-inflammatory agent is ketoprofen.

25. The formulation of claim **1** further containing an antiemetic agent.

26. The formulation of claim **1** further containing an antipileptic agent.

27. The formulation of claim **1** further containing a corticosteroid.

28. The formulation of claim **1** further containing a tricyclic antidepressant.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,028,222
APPLICATION NO. : 09/051246
DATED : February 22, 2000
INVENTOR(S) : François Dietlin et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1, line 21, "hydrolysed" should be -- hydrolyzed --

Column 1, line 35, "Arrenium" should be -- Arrhenius --

Column 1, line 67, "p-aminophen" should be -- p-aminophenol --

Column 2, line 1, "19,8%" should be -- 19.8% --

Column 2, lines 26-27, "alca-nol" should read -- alka-nol --

Column 2, line 50, "cystein, acetylcystein" should read -- cysteine, acetylcysteine --

Column 2, line 51, "dithlothritol" should read -- dithiothreitol --

Column 2, line 61, "cystein, reduced slate" should read -- cysteine, reduced state --

Column 2, line 62, "N-acetylcystein" should read -- N-acetylcysteine --

Column 3, line 27, "ou" should be -- or --

Column 3, line 28 "hydrogene" should be -- hydrogen --

Column 3, line 31 "betwenn" should be -- between --

Column 4, line 23, "AINS" should be -- NSAID --

Column 4, line 44, "1000 ml" should read -- 1.000 ml --

Column 5, line 47 (table), "codein" should read -- codeine --

Column 5, line 55 (table), "q.s. 1000 ml", all three occurrences, should be -- q.s. 1.000 ml --

Signed and Sealed this

Thirtieth Day of November, 2010

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

Column 6, line 11, "recristallization" should read -- recrystallization --

Column 6, line 12, "6,25 ml" should read -- 6.25 ml --

Column 6, line 23 (table, column 3), "codein" should read -- codeine --

Column 6, line 24 (table), "codein sulfate" should read -- codeine sulfate --

Column 6, line 34 (table), next to last line, "q.s.f. 1000 ml", all three occurrences, should be --q.s.f. 1.000 ml --

Column 7, line 32, "recristallization" should read -- recrystallization --

Column 7, line 35, "cristals" should read -- crystals --

Column 7, line 36, "cristal" should read -- crystal --

Column 7, line 36, "cristallization" should read -- crystallization --

Column 7, line 44, "is" should read -- in --

Column 7, line 63, Table 1.2, "sorbital" should read -- sorbitol --

Column 9, Table 4.1, last line, "q.s.f. 1000 ml", should read -- q.s.f. 1.000 ml --

Column 10, line 12, "cristallization" should read -- crystallization --

Column 10, line 31, "oxydation" should read -- oxidation --

Column 10, line 44, "oxydative" should read -- oxidative --

Column 10, line 62, "of type of the type" should read -- of the type --

Column 10, line 66, "acetylcystein>paracetamol+cystein" should read
-- acetylcysteine>paracetamol+cysteine --

Column 11, line 16, in table 3.1, "q.s. 1000 ml" should read -- q.s. 1.000 ml --

Column 11, lines 21-22, "7,0 (5,8)-8,0 (8,7)-8,5 (7,1)-9,0 (97,5)-9,5 (8,0)-10,0 (8,5)" should read
-- 7.0 (5.8)-8.0 (8.7)-8.5 (7.1)-9.0 (7.5)-9.5 (8.0)-10.0 (8-5) --

Column 11, line 36, "7,5 to 9,5" should read -- 7.5 to 9.5 --

Column 11, line 38, "pH 7,0 (actual pH 5,8)" should read -- pH 7.0 (actual pH 5.8) --

Column 11, line 51, in table 3.2, "q.s.f. 1000 ml" should read -- q.s.f. 1.000 ml --

Column 11, line 56, "pH 5,0-7,0" should read -- pH 5.0-7.0 --

Column 11, line 66, "pH 6,0 and 5,0" should read -- pH 6.0 and 5.0 --

Column 12, line 20, in table 4.2, "q.s.f. 1000 ml", both occurrences, should read -- q.s.f. 1.000 ml --

Column 12, line 24, "pH 6,0" should read -- pH 6.0 --

Column 12, line 48, "tainter" should read -- fainter --

Column 13, line 8, in table 5.1, "q.s.f. 1000 ml" should read -- q.s.f. 1.000 ml --

Column 13, line 31, "cystein" should read -- cysteine --

Column 13, lines 50-51, in table 5.2, "q.s.f. 1000 ml" should read -- q.s.f. 1.000 ml --

Column 14, line 18 (in the table), "cystein" should read -- cysteine --

Column 14, line 31 (in the table), "cystein" should read -- cysteine --

Column 14, line 34 (in the table), "cystein" should read -- cysteine --

Column 14, line 37 (in the table), "acetylcystein" should read -- acetylcysteine --

Column 14, line 54 (in the table), "codein" should read -- codeine --

Column 14, line 59, in table 6.1, "q.s.f. 1000 ml" should read -- q.s.f. 1.000 ml --

Column 15, line 32, in the table, "codein" should read -- codeine --

Column 15, line 37, in table 6.2, "q.s.f. 1000 ml" should read -- q.s.f. 1.000 ml --

Column 15, line 47, "cystein" should read -- cysteine --

Column 15, line 49, "codein" should read -- codeine --

Column 16, line 12 (in the table), "acetylcystein" should read -- acetylcysteine --

Column 16, line 13 (in the table), "cystein" should read -- cysteine --

Column 16, line 21, "codein" should read -- codeine --

Column 16, line 27 (in the table), "codein" should read -- codeine --

Column 16, line 31 (in the table), "codein" should read -- codeine --

Column 16, line 32 (in the table), "cystein" should read -- cysteine --

Column 16, line 35, "one one hand" should read -- on one hand --

Column 16, line 53, in table 7.1, "q.s.f. 1000 ml" should read -- q.s.f. 1.000 ml --

Column 17, line 24, in table 7.2, "q.s.f. 1000 ml" should read -- q.s.f. 1.000 ml --

Column 17, line 28, "7,6" should read -- 7.6 --

Column 19, line 2, claim 6, "ar" should read -- are --

Column 19, line 12, claim 8, "cystein, acetlcystein" should read -- cysteine, acetylcysteine --

EXHIBIT B

US006992218B2

(12) **United States Patent**
Dietlin et al.

(10) **Patent No.: US 6,992,218 B2**
(45) **Date of Patent: Jan. 31, 2006**

(54) **METHOD FOR OBTAINING AQUEOUS FORMULATIONS OF OXIDATION-SENSITIVE ACTIVE PRINCIPLES**

(75) Inventors: **Francois Dietlin**, La Vesinet (FR); **Daniele Fredj**, Gif sur Yvette (FR)

(73) Assignee: **Pharmatop SCR** (FR)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/332,060**

(22) PCT Filed: **Jun. 6, 2001**

(86) PCT No.: **PCT/FR01/01749**

§ 371 (c)(1),
(2), (4) Date: **Aug. 4, 2003**

(87) PCT Pub. No.: **WO01/93830**

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(30) **Foreign Application Priority Data**

Jun. 6, 2000 (FR) 00 07231

(51) **Int. Cl.**
C07C 209/90 (2006.01)

(52) **U.S. Cl.** **564/4**; 564/5; 564/6; 564/7; 564/223; 514/617

(58) **Field of Classification Search** 564/4, 564/5, 6, 7, 223; 514/617
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,028,222 A * 2/2000 Dietlin et al. 564/4

* cited by examiner

Primary Examiner—Shailendra Kumar
(74) *Attorney, Agent, or Firm*—Charles A. Muserlian

(57) **ABSTRACT**

A method for obtaining aqueous formulations with easily oxidizable active principles, notably phenols, stable over a prolonged period, comprising subjecting them to extreme deoxygenation by bubbling with an inert gas and/or placing wider vaccum, protecting them against possible resorption of oxygen by keeping them under an inert gas atmosphere, by filling, under inert gas, into bottles previously cleared of air by insufflation with inert gas, then subjecting them, while stoppering, to low pressure as obtained in the bottle, of 65,000 Pa maximum, to obtain aqueous solutions having a residual oxygen concentration in the solution below 2 ppm, and preferably of the order of 1 ppm and even 0.5 ppm useful as injectable preparations having an oxygen concentration in the solution below 2 ppm.

19 Claims, No Drawings

METHOD FOR OBTAINING AQUEOUS FORMULATIONS OF OXIDATION-SENSITIVE ACTIVE PRINCIPLES

This application is a 371 of PCT/FR01/01749 filed Jun. 6, 2001.

The object of the present invention is a new method for producing injectable aqueous solutions with active principles, in particular active principles which are useful in therapeutics and susceptible to oxygen, and also a procedure for preparation of these methods of packaging, and their utilization.

Its object is, more precisely, a new method for aqueous formulations with active principles susceptible to oxidation which can notably be utilized in injectable preparations being stable over a long period, and containing, for example, phenolic or polyphenolic substances, amino alcohols or sulphur-containing substances.

Aqueous solutions with active principles traditionally have different applications, notably in therapeutics, in particular in the form of injectable solutions intended for humans or animals. However, it happens that some of these active principles present problems of stability in solution. These problems may be connected with the fact that the active principles are susceptible to oxidation and form undesired degradation products by reaction with the oxygen in the air, or above all with the oxygen dissolved in the aqueous solution. Other active principles are indirectly susceptible to oxygen, i.e. whilst being kept they are likely to form, by chemical reactions, oxidizable derivatives. These derivatives, by reacting with oxygen, then lead to the formation of undesired secondary products. This is the case, in particular, with paracetamol. The Applicants have, in fact, demonstrated the fact that paracetamol, in aqueous solution, undergoes hydrolysis on the one hand, and on the other hand, degrades to form a quinone-imine susceptible to polymerization into nitrogenous polymers. The derivatives resulting from these reactions are themselves also susceptible to oxidation and form undesired secondary products.

The secondary products formed by reaction of the oxygen with these active principles, or their derivatives, leads to numerous disadvantages such as, for example, a loss of activity or the production of allergenic products.

In fact, as a result of degradation by oxidation, the titre of active principle in the aqueous solution is considerably reduced, in an uncontrollable manner, and poses a major problem, especially when these solutions are used in therapeutics, more particularly in the form of injectable solutions, when it is important that the dose of active principle is precisely determined.

Moreover, the oxidation products lead to the formation of coloured compounds, thus making the aqueous solution unsuitable for therapeutic applications.

In addition, the formation of secondary products may further increase as a result of a rise in temperature, which, consequently, may cause heat-sterilization of the aqueous solutions with these active principles, impossible, or at least difficult.

Here and in the following text, the term "phenolic active principle susceptible to oxidation" means any substance, which may or may not be medicinal, comprising a phenolic structure and/or functions supported by the phenolic structure which react easily with oxygen, and which degrades forming oxidation products, coloured or colourless, or hydrolysis products or polymerization products.

The active principles susceptible to oxygen are essentially organic substances bearing oxidizable functions,

amongst which the following may in particular be cited: phenols, polyphenols, aminophenols, phenolic alcohols and phenolic ketones, as well as aromatic amines or partially hydrogenated cyclical structures such as derivatives of anthraquinone. The following ones may also be cited:compounds with an enolic structure or with an aldehyde function, or a ketone function or an alcohol function.

Aminosides which are also susceptible to the presence of oxygen may also be cited.

Amongst the easily oxidizable active principles that will be incorporated into the aqueous solutions of the invention, the following may be cited more particularly: phenols or aminophenols, such as paracetamol, epinephrine, norepinephrine, adrenalone, isoprenaline, orciprenaline, isoxuprine, phenylephrine or dobutamine; the following will be cited as aromatic amines: procaine, bupivacaine, tetracaine, butoform, L-dopa or Carbidopa; the following one will be cited as aminoketones:Propaphenone; the following ones will be cited as aminoglucosides: the gentamycines, amikacine, dibekacine, netilmycin, sisomycin, tobramycin, micronomycine; as phenothiazines, promethazine; as hydroaromatic molecules, riboflavin, 9-amino dihydro acridine; further cortisonic derivatives may be cited, such as dexamethasone, betamethasone, triamcinolone, fluocinonide, flunisolide, fluocinolone acetonide, fluocortolone, Clobetasone and their derivatives, beclometasone and its esters; Tetracycline derivatives, such as Doxycycline or Minocycline.

For the purpose of improving the stability of such medicinal active principles which are susceptible to oxidation, and thus to overcome the disadvantages described above, a proposal has already been made to prevent the action of the oxygen, either by eliminating the oxygen, or by neutralizing it, or again by combining both these types of operation.

Several methods have been used for this purpose:

a) elimination of the oxygen by raising the temperature of the aqueous solution, by putting the aqueous solution under vacuum or by bubbling an inert gas such as nitrogen, carbon dioxide or argon through the solution.

However these methods have the disadvantage of allowing only a partial and insufficient elimination of the oxygen, or requiring a considerable amount of time. The bubbling of nitrogen, the method most practised within the pharmaceuticals industry, only allows the oxygen content to be reduced to values of the order of 2 ppm maximum.

b) neutralization of the oxygen dissolved in the aqueous solution, by the addition to the latter of an antioxidant such as a thiol or sulphur anhydride derivatives such as the sulphites, bisulphites or alkali metal metabisulphites.

c) a combination of the elimination of oxygen and the addition of an antioxidant. A method of this type has been described by the Applicants in the French patent 2.751.875.

All the above methods have a certain efficacy. However, oxygen shows a very great facility to dissolve in water, making it necessary to ensure that the solution, once deoxygenated, does not subsequently come into contact with atmospheric air, otherwise the advantage of having previously eliminated the oxygen will be lost.

Within the framework of the industrial manufacture of injectable solutions, it has been easy to deoxygenate bulk solutions in air-tight tanks and thus to keep them away from the air. However, during subsequent bottle or bag filling and packaging operations, it is difficult to keep the solutions totally away from air. In spite of precautions that may be taken for this purpose, especially filling and packaging the

bottles with the addition of inert gas, once packaged, the solutions can may once again contain, or fix, or take up significant quantities of dissolved oxygen.

If these solutions have to be heat-sterilized, especially at high temperatures in the region of 120° C., the residual quantity of dissolved oxygen can easily react with the active principle susceptible to oxidation, resulting in its total or partial degradation.

In effect it has been found that the presence of any oxygen is harmful and that infinitesimal quantities are sufficient to bring about an oxidation reaction, especially at sterilization temperature. The residual oxygen concentration limit present in the medium, likely to produce an oxidizing effect, is of the order of 2 ppm.

The applicants have thus made use of a method for stabilizing of the solutions of phenolic, easily oxidizable substances, in which deoxygenation has previous been completed to a degree that would avoid the possibility of this degradation occurring.

It is known, moreover, that the utilization of antioxidants is not always purely advantageous. Thus, the antioxidants used gradually degrade, which makes it necessary to add relatively large quantities of them to ensure satisfactory protection of the active principle.

It is also possible to combine the elimination of oxygen with the addition of an antioxidant.

Complementary tests have shown that the problem of stabilization of the formulations according to the invention was appreciably more complex than anticipated, and it has notably been established that, without antioxidant, an essentially deoxygenated solution became pink in colour after a certain time at ambient temperature. In this respect it has been observed that injectable solutions which are not completely deoxygenated do not become appreciably coloured if an α-hydroxypolycarboxylic acid is previously added to the solution, in particular the addition of citric acid, or an alkaline citrate, or a mixture of the two, makes it possible to slow down the appearance of a coloration.

In addition, it has emerged that it is possible to complete the deoxygenation of a solution of a substance susceptible to oxidation by the use of vacuum. This results is a greater stability of the antioxidant and less formation of secondary products resulting from oxidative degradation, notably after several sterilization cycles.

The α-hydroxypolycarboxylic acids and their salts, play an important role. They do not act by stabilizing the pH, nor by playing a role capturing free radicals. They advantageously replace polyhydroxylated compounds such as sorbitol or mannitol.

In the particular case of paracetamol, a mixture of trisodic citrate and citric acid is preferably used, in a quantity sufficient to obtain a pH value of the order of 5 to 6, and preferably 5.5.

The object of the present invention is therefore a procedure for preparation of formulations of aqueous solutions with phenolic active principles, in particular active principles susceptible to oxidation, like paracetamol, making it possible to confer a high degree of stability over the course of time.

A further object of the present invention consists of the utilization of these formulations for the production of injectable aqueous solutions intended for humans or animals, containing an added phenolic active principle to which an anti-inflammatory agent and/or central analgesic may or may not be added.

The object of the invention is specifically a method for producing an aqueous formulations containing easily oxidizable phenolic active principles, which are stable over a long period of time, possibly containing antioxidants, characterized in that they are obtained by submitting them to extreme deoxygenation either by bubbling of an inert gas, or by placing under vacuum, then protecting them from possible resorption of oxygen during the course of production, by keeping them in an inert gas atmosphere, by packaging them into bottles previously cleared of air by insufflation with inert gas, and notably topping gas which is heavier than air, such as argon, then in that, at the moment of stoppering, they are subjected to a reduction in pressure, so that a pressure is obtained, which is lower than atmospheric pressure, of 65,000 Pa maximum, preferably between 5,000 and 50,000 Pa, to obtain an aqueous solution having an oxygen concentration in the solution below 2 ppm.

According to another aspect of the invention, the invention consists of a method for preparing of a formulation as previously described, which includes the following stages:

a) an aqueous solution with at least one active principle is subjected to extreme, and possibly complete, deoxygenation,

b) under an inert gas atmosphere, part or all of the deoxygenated aqueous solution is introduced into a container previously cleared of the air contained therein,

c) the container is stoppered under an inert gas atmosphere, in such a way as to create within the container a maximum pressure of 65,000 Pa.

The aqueous solution is preferably deoxygenated by bubbling through an inert gas, such as nitrogen. The bubbling process can be continued until a content of less than 2 ppm is obtained, preferably a content of 1–0.5 ppm, and particularly even 0.05 ppm of oxygen in the aqueous solution. The deoxygenated solution thus obtained can then be conveyed, safe from the air, into a filling machine, to be distributed into containers such as flasks, ampoules or bottles.

The aqueous solution is introduced into the container under an inert gas atmosphere, such as nitrogen. Before the aqueous solution with active principle is introduced into the container, the latter is cleared of the air contained therein, for example by insufflation of an inert gas, preferably an inert gas heavier than air, such as argon, so that the latter is not immediately replaced by air in accordance with Archimedes' principle.

Once the containers have been filled, with constant insufflation of an inert gas, the bottles are stoppered under an extreme vacuum to keep them, after stoppering, at a pressure of 65,000 Pa or below, preferably between 5,000 et 50,000 Pa. To do this, known means can be utilized, such as placing a vacuum bell-jar over the neck of the container, immediately after the stopper is put in. After being placed in hermetic contact, the inside of the bell-jar is placed under a vacuum, for example by linking it to a container under vacuum. The stopper of the container is raised and the gas rising above the solution is aspirated. The stopper is then replaced in the container and the latter can be hermetically sealed, for example by fitting on a capsule, then crimping. The container, once stoppered, can be subjected to a sterilization process, in particular sterilization by autoclaving or irradiation.

The aqueous solution containing an active principle can be subjected to sterilization by sterilising filtration before this solution is introduced into the container. The solution is then introduced into the container, preferably under aseptic conditions, under an inert gas, the latter advantageously being sterile.

The inert gas preferably used in the method according to the invention for bubbling is nitrogen, that used for topping is argon, which is heavier than air. Xenon or neon can also be used.

After the bottles have been filled, with constant insufflation of an inert gas, with the solution of easily oxidizable substance, the bottle is stoppered under an extreme vacuum, to maintain in the bottles after stoppering, a low pressure of more than 300 mm of mercury, or a maximum pressure of 65,000 Pa.

According to the invention procedure, the low pressure prevailing in the bottle promotes the elimination of the oxygen still present in the solution and this constitutes a distinct advantage.

This elimination makes it possible to reduce the quantity of antioxidant necessary for protection of the active principle, or even avoid adding it. It also allows heat-sterilization of solutions that could not be sterilized previously due to degradation of the active principle and/or antioxidant by oxidation during this operation. This reduction in the quantity of antioxidant may also allow these solutions to be stabilized for longer periods.

Thus, French patent 2.751.875 mentions that aqueous solutions of paracetamol are stable for 48 hours at ambient temperature, under light, and at 70° C. in darkness, if they are subjected to bubbling with nitrogen, filling under nitrogen and the addition of an antioxidant. It is possible to obtain stability of longer duration, by using the procedure described, as shown by the following examples.

The antioxidant that it may be appropriate to add to the medium is a sulphite, or sulphite derivative, a thiolic substance such as, for example, cysteine, acetylcysteine, dithiothreitol or α-thioglycerol, thiomalic acid, thioglycerol, methionine; a hydroxylated substance such as ascorbic acid, iso-ascorbic acid, mannitol, sorbitol, a ethylenically unsaturated substance such as sorbic acid, undecylenic acid or fumaric acid or a hydroxy polycarboxylic acid, or a reducing sugar such as trehalulose, maltulose or isomaltulose.

Moreover, it has been found that the addition of a hydroxypolycarboxylic acid in conjunction with, or instead of the deoxygenation operation, has the effect of appreciably reducing the consumption of antioxidant and leads to a reduction in the concentration of antioxidant. The quantity of antioxidant that it may be appropriate to add is low, preferably ranging from 0,1 mg to 1 000 mg per litre of solution, and preferably from 0,2 to 20 mg.

It may also be advantageous to add a pH regulation agent, and in particular a buffering agent, especially when the easily oxidizable phenolic active principles are susceptible to being degraded or hydrolysed within particular pH ranges. It may thus be appropriate to adjust the pH of the solutions between 4 and 8 and particularly between 4.5 and 6.0 where the oxidizability of the phenolic molecules will be lower. An appropriate buffer will be, for example, a sodium hydrogenophosphate/hydrochloric acid mixture, sodium hydrogenophosphate/sodium hydroxide mixture, disodic phosphate/phosphoric acid mixture, acetic acid/sodium acetate mixture, citric acid/sodium citrate mixture, or trisodic citrate/hydrochloric acid mixture. The choice of pH will depend mainly on the nature of the active principle and its character of oxydizability.

The formulations according to the invention are utilized in the field of therapeutics in injectable form administered directly or added to a perfusion bag as an analgesic or an antibiotic or as a cardio-vascular drug. The injectable solution of paracetamol according to the invention is distinguished by quite remarkable analgesic properties. It may in addition contain a vasoconstrictor such as adrenalin or a central analgesic such as codeine or d-propoxyphene or an anti-inflammatory agent such as tiaprofenic acid or one of its salts.

Preparation of such a solution is carried out under nitrogen. The dissolved oxygen concentration is less than 0.05 ppm.

It is also possible to use as hydroxypolycarboxylic acid, tartaric acid or an alkaline monotartarate such as sodium salt or potassium salt in the presence of a dimetallic tartarate to obtain a pH value of the order of 5.5. It has also been noted that in the presence of hydroxypolycarboxylic acid, the pH is much more stable. The same is true for other hydroxypolycarboxylic acids such as gluconic acid, saccharic acid, citramalic acid or malic acid.

It is also possible only to use a hydroxypolycarboxylic acid salt such as trisodic citrate or disodic tartarate and adjust the pH by the moderate addition of hydrochloric acid.

The addition of hydroxypolycarboxylic acid and notably citric acid, at concentrations that make it possible to obtain a pH value of the order of 5.5, plays an important role. It has been shown that concentrations ranging from 5 to 200 mg per 100 ml ensure effective protection against oxidation (absence of coloration) and protection against degradation of the antioxidant attested by a lower content of degradation products of the cysteine used as an antioxidant.

In particular, in the case of paracetamol, after the addition of trisodic citrate at a concentration of 70 mg/100 ml of solution, the residual cysteine concentration is approximately double than that of preparations without citrate, no coloration appeared, even after 7 weeks at 40° C., and there was no variation in the concentration of paracetamol.

In conclusion, the four parameters that have to be taken into consideration as essential for preservation following heat sterilization of aqueous formulations with an active principle susceptible to oxidation are, taken separately or in combination:

- complete deoxygenation by bubbling with inert gas below an oxygen concentration of less than 2 ppm,
- completed by the possible addition of an antioxidant,
- the addition of a hydroxypolycarboxylic acid,
- and the introduction of the aqueous solutions under an atmosphere of inert gas such as argon into a container from which the air has previously been removed.

Under these conditions, the concentration of active principle does not undergo any variation and the absence of oxidation can be established by maintaining colourless solutions for a prolonged period of time.

EXAMPLE I

Production of an Aqueous Compound of Paracetamol

A paracetamol solution is prepared in water at a concentration ranging from 2 to 50 mg/ml. Extreme deoxygenation to less than 2 ppm was carried out by bubbling with inert gas, then placing in bottles under inert gas and under vacuum (less than 65,000 Pa of residual pressure). Thus a residual concentration of oxygen is maintained in the solution, of less than 2 ppm and preferably below 1 ppm.

The pH of the solution is between 4 and 8, and preferably 4.5 to 6.0. For this purpose a buffer system is added, adjusted to 5.5.

The addition of an antioxidant contributes to the stability of the solution. The preferred antioxidants are: ascorbic acid, an ascorbate, a thiol, a polyol or a hydroxypolycarboxylic acid.

The preferred antioxidant is the cysteine sodium citrate mixture.

An isotonizing agent can be added to the solution.

EXAMPLE II

Production of an Aqueous Compound of Paracetamol without Antioxidant (Example for Comparison)

A 10 mg/ml aqueous paracetamol solution is prepared. Adjustment to pH 5.5 is carried out by the addition of HCl, and buffering by the addition of sodium hydrogenophosphate.

Deoxygenation is then carried out by bubbling with nitrogen, until a residual oxygen content of approximately 0.2 ppm is obtained. After the bottles are filled with the solution during prolonged bubbling with nitrogen, they are sterilized at 121° C. for 15 minutes.

After being kept at 25° C. for 6 months, the solution is still colourless, there is no change in the paracetamol content, and the content of degradation products of paracetamol determined by HPLC remains lower than 0.015% of the paracetamol.

In another test, the paracetamol solution, after being subjected to bubbling with nitrogen, has been packaged under nitrogen. When the bottles of solution are stoppered, a vacuum is applied, to obtain a residual pressure of less than 10,000 Pa The residual dissolved oxygen content was 0.16 ppm. After sterilization at 121° C. for 15 minutes, and after being kept for 8 days at 30° C., the solution remained colourless.

It thus appears that the essential means is deoxygenation to below a residual concentration of the order of 0.2 ppm and this means makes it possible to obtain complete preservation for a prolonged period. The possible presence of an antioxidant completes the effect of the deoxygenation but does not replace it.

EXAMPLE III

Production of an Aqueous Solution of Paracetamol Containing Citrate Ions

It has been established that aqueous solutions of paracetamol containing slightly higher residual concentrations of oxygen, i.e of the order of 0.3 to 0.4 ppm, keep less well due to the fact that the paracetamol can react with very small quantities of oxygen and can form coloured compounds.

Thus a 10 mg/ml paracetamol solution adjusted to pH 5.5 by hydrochloric acid was subjected to bubbling with nitrogen until an oxygen content of approximately 0.4 ppm was obtained. The bottles were sterilized at 121° C. for 15 minutes and kept at ambient temperature. After being kept for 9 days, a yellow-pink coloration was observed in the paracetamol solution.

Conversely, if a stabilizing agent in the form of a mixture of citric acid and sodium citrate is added to a composition identical to the above, adjustment of the pH to 5.5 occurs spontaneously and it is not necessary to add hydrochloric acid. After bubbling with nitrogen, the residual oxygen content is of the order of 0.4 ppm. Afterwards the solution is packaged into bottles under vacuum and sterilized at 121° C. for 15 minutes. The bottles are kept for 67 days at ambient temperature. The solution remains perfectly colourless.

This result is unexpected, as the action of the citrate ion cannot be related either to the antioxidants' complexing properties, nor to their reinforcing properties. Moreover, the particular effect of the citrate ion cannot be related to an antioxidizing action.

EXAMPLE IV

Stabilization of Partially Deoxygenated Aqueous Paracetamol Solutions

For greater residual oxygen contents, that may reach 1.5 ppm, it is preferable to resort to the addition of a stabilizing agent with more powerful antioxidant properties such as a sulphite, a thiol derivative or an ascorbate.

A 10 mg/ml aqueous paracetamol solution adjusted to pH 5.5 by sodium hydroxide and buffered at this value by sodium acetate was made isotonic by a sufficient quantity of sodium chloride, then an antioxidant is added to it, in this case 0.20 mg/ml cysteine chlorhydrate. This solution was subjected to bubbling with nitrogen then placed under vacuum (low pressure approx. 550 mm of Hg) before stoppering the bottles. The residual oxygen content amounted to approx. 1.5 ppm of dissolved oxygen. After sterilization, the bottles containing this solution were kept for 24 months at 25° C. The bottles remained colourless after this period, the paracetamol content was 100% of the original value, and the degradation products of the paracetamol measured by HPLC represented less than 0.02% of the paracetamol content.

The presence of an antioxidant thus played an important role. In the paracetamol solution, the antioxidant, like cysteine, reacts with the dissolved oxygen by taking the place of the phenolic molecule that is to be protected.

However, after being kept the cysteine almost completely disappeared and cystine is formed, which is the major oxidation product of cysteine.

EXAMPLE V

Buffered and Stabilized Aqueous Paracetamol Solutions

Knowing that citrate ions have a stabilizing effect with regard to paracetamol, it was desirable to check whether this effect could be explained by a protective action vis-à-vis the antioxidant, such as cysteine.

A 0.25 mg/ml aqueous cysteine solution was adjusted to pH 5.5, made isotonic by sodium chloride and buffered using as a buffering agent: dehydrated sodium citrate (0.70 mg/ml), sodium acetate, sodium hydrogenophosphate, in quantities equimolar to that of the citrate.

These solutions which involved neither bubbling with nitrogen, nor being placed under vacuum, contained approx. 7 ppm of dissolved oxygen. They were kept in darkness at 25° C. for 3 days.

The dosages carried out showed that the lowest residual cysteine content is found either in non-buffered solutions (15%), or in the presence of citrate. In contrast, in the presence of acetate (18%) or hydrogenophosphate (21%) it is higher.

It follows that the citrate ions do not have any particular protective effect vis-à-vis an antioxidant such as cysteine.

EXAMPLE VI

Preparation of Buffered Paracetamol Solutions

In this test, paracetamol, cysteine and a buffer were brought together. A quantity of sodium citrate (in the form of dihydrated disodic citrate) was added to 10 mg/ml aqueous paracetamol solutions, made isotonic by NaCl and stabilized by the addition of cysteine hydrochlorhide (0.25 mg/ml) suitable for adjusting the pH to 5.5. A quantity of citrate of the order of 0.7 mg/ml is sufficient. Comparative solutions were prepared without sodium citrate or replacing the citrate ions by equimolar quantities to those of the citrate, of either sodium acetate, or sodium hydrogenophosphate; in all cases adjusting the pH to a value of 5.5 by the addition of sodium hydroxide or hydrochloric acid.

The solutions were not subjected to bubbling with inert gas (nitrogen) and were kept in darkness at 25° C. for 3 days.

The presence of residual cysteine is thus established in increasing quantities, in the non-buffered solution (42%), in the presence of sodium acetate (17%), in the presence of sodium hydrogenophosphate (21%) and in the presence of citrate (22%) respectively.

After being kept for 20 days, all the solutions were strongly coloured with the exception of the solution containing citrate ions, which had remained colourless. It is established that in the presence of paracetamol, cysteine is protected by the presence of citrate, whilst in the absence of citrate, the cysteine has no protective effect.

Table 1 below illustrates the conclusions set forth above:

The experiments thus evidence the interactions in the presence of different oxygen contents:

Solution	Oxygen content	Results
Paracetamol alone	0.2 ppm	No degradation of the paracetamol
Paracetamol + citrate	0.4 ppm	No degradation of the paracetamol
Paracetamol + cysteine	1.5 ppm	No degradation of the paracetamol
Cysteine + citrate	7 ppm	No protection of the cysteine
Paracetamol + cysteine + citrate	7 ppm	Protection of paracetamol and cysteine

Unexpectedly, it was by bringing together paracetamol, cysteine and citrate that the best preserving properties were obtained, both for cysteine and for paracetamol even in the presence of oxygen.

The same tests were repeated with more highly concentrated paracetamol solutions.

Constituent	Paracetamol alone (P)	Paracetamol + citrate (PC)	Paracetamol + citrate + cysteine (PCC)
Paracetamol	1 g	1 g	1 g
Sodium citrate	0	0.070 g	qsp pH 5.5 (i.e. 0.07 g of citrate)
Chlorhydrate cysteine	0	0	0.025 g
NaCl	0.09	0.09	0.09 g
HCl or NaOH	qsp, pH 5.5	qsp pH 5.5	0
Inert gas	qsp O_2 approx. 0.5 ppm	qsp O_2 approx. 0.5 ppm	qsp O_2 approx. 0.5 ppm
Water	qsp 100 ml	qsp 100 ml	qsp 100 ml

Packaging: under nitrogen (A) or under residual pressure of approx. 10,000 Pa

Sterlization at 121° C. for 15 minutes.

Results (after Sterilization):

a) the solutions P:PV (under vacuum) and PA (under nitrogen) are pink;

b) the solutions PC:PCV (citrate) are colourless and PCA (under nitrogen) is pink;

c) the solutions PCC:PCCV and PCCA are colourless but the residual cysteine content is higher when PCV is used.

Conclusion

For residual oxygen contents of the order of 0.5 ppm, the vacuum is in itself insufficient to ensure the stability of the paracetamol.

On the other hand, it acts synergically with citrate both with regard to the keeping properties of paracetamol and of cysteine.

EXAMPLE VII

Stability of Paracetamol Solution, and of Paracetamol Solution to which Sodium Citrate has been Added in the Presence of Nitrogen, or of Nitrogen Under a Vacuum

Preparation of the solutions:

Constituent	Paracetamol (P)	Paracetamol – Citrate (PC)
Paracetamol (mg)	1,000	1,000
Trisodium citrate, $2H_2O$ (mg)	—	70
NaCl (mg)	700	700
HCl q.s.p. pH	5.50	5.50
H_2O q.s.p. (ml)	100	100

The solutions are produced under nitrogen (<0,50 ppm). Filling takes place under nitrogen, of volumes of 80 ml, into 100 ml bottles. Nitrogen is bubbled into the bottle for 30 seconds before stoppering.

Half the bottles are placed under an extreme vacuum before stoppering.

The solutions are heat sterilized at +120° C. for 15 minutes.

The solutions are stabilized at +25° C. and at +40° C.

Analysis at T=0

Solution	Oxygen (ppm)	Residual pressure in Pa	pH
Paracetamol/nitrogen, not sterilized	0.40	—	5.92
Paracetamol/nitrogen, sterilized	0.34	—	6.03
Paracetamol/vacuum, not sterilized	0.55	<10,000	5.98
Paracetamol/vacuum, sterilized	0.50	<10,000	6.28
Paracetamol/Citrate/Nitrogen, not sterilized	0.50	— —	5.50
Paracetamol/Citrate/Nitrogen, sterilized	0.60		5.53
Paracetamol/Citrate/vacuum, not sterilized	0.36	<10,000	5.50
Paracetamol/Citrate/vacuum, sterilized	0.40	<10,000	5.54

HPLC analysis does not show the presence de peaks corresponding to degradation products (<0.01%).

Appearance of the Solutions after Keeping in Darkness at 25° C. for 2 Months

Solution	coloration on D9	coloration on D13	coloration on D21	coloration on D26	coloration at 1 month	coloration at 2 months
Paracetamol/ Nitrogen sterilized	colourless	colourless	yellow hue	yellow hue	yellow +	yellow +
Paracetamol, placed under vacuum sterilized	colourless	colourless	colourless	colourless	colourless	yellow hue
Paracetamol/Citrate/ Nitrogen, sterilized	colourless	colourless	colourless	yellow hue Paracetamol/ Nitrogen	yellow hue	yellow +
Paracetamol/Citrate/ placed under vacuum, sterilized	colourless	colourless	colourless	colourless	colourless	colourless

Conclusion

Only the citrate+vacuum combination ensures complete preservation of the paracetamol.

EXAMPLE VIII

Stability of the Paracetamol Solutions Protected by Sodium Citrate and Cysteine for Oxygen Concentrations of Approx. 1 ppm

Composition of the Solution

Constituent	Quantity
Paracetamol (g)	1
Cysteine HCL, H20 (mg)	25
Sodium citrate, H20 (mg)	70
Sodium chloride (mg)	700
Water enough for	100 ml

Preparation of the solution takes place with continuous bubbling with nitrogen. It is filled into 100 ml bottles, under nitrogen, until a solution containing between 0.7 and 1.0 ppm of oxygen is obtained.

The bottles are then stoppered under a nitrogen atmosphere or under vacuum (approx. 10,000 Pa). Following sterilization at 121° C. for 15 minutes, the bottles are kept in darkness at 40° C. The colouration, the pH, the oxygen content and the residual cysteine content are evaluated immediately after sterilization, then after being stored for 14 days.

Results

Solution	Coloration	pH	Oxygen (ppm)	Residual cysteine (%)
Solution under nitrogen, after sterilization	colourless	5.53	0.85	75
Solution under vacuum, after sterilization	colourless	5.51	0.90	85
Solution under nitrogen, after 14 days at 40° C.	yellow	5.58	0.60	27
Solution under vacuum, after 14 days at 40° C.	colourless	5.59	0.90	85

Conclusion

Keeping under vacuum has a protective effect on the Paracetamol and the cysteine when the solution is kept under conditions of accelerated degradation. Conversely, preservation is insufficient under nitrogen. The vacuum seems to inhibit the oxidation reaction of the paracetamol and the cysteine, which confirms the reduction in residual oxygen under nitrogen, as compared with the maintenance of residual oxygen under vacuum.

EXAMPLE IX

1% Dobutamine Sulphate Solution

A Dobutamine sulphate solution is prepared by dissolving 1 g Dobutamine in 50 ml of water and 19 ml of a 0.10% sodium ascorbate solution is added, with continuous bubbling of nitrogen. Then 25 mg hydrated cysteine chlorhydrate and 70 mg hydrated sodium citrate are added, then 700 mg sodium chloride to ensure isotonicity. The solution is made up to 100 ml by the addition of distilled water for injectable preparations.

It is filled into 100 ml bottles under nitrogen until the residual oxygen content is below 0.8 ppm. The bottles are then stoppered under vacuum (approx. 10,000 Pa) and sterilized at 121° C. for 20 minutes.

After removal from the autoclave, the bottles are kept in darkness in a thermostatic cupboard at 50° C.

An evaluation is made of absorption at 308 nm as an indication of oxidation into secondary products, the residual oxygen content and the residual cysteine content immediately after sterilization, then after being kept for 14 days at 50° C.

Results

There is no degradation of the Dobutamine in heat.

Using liquid chromatography the appearance of secondary peaks is established, detected by measuring the absorption at 308 nm, the degree of which decreases as the pH increases. Coloration remains slight and reduces as the pH increases.

What is claimed is:

1. A method for preparing an aqueous solution with an active nature susceptible to oxidation, which is paracetamol, while preserving for a prolonged period, comprising deoxygenation of the solution by bubbling with at least one inert gas and/or placing under vacuum, until the oxygen content is below 2 ppm, and optionally the aforementioned aqueous solution with an active principle is topped with an inert gas atmosphere heavier than air and placed in a closed container in which the prevailing pressure is 65,000 Pa maximum, and the oxygen content of the aqueous solution is below 2 ppm, and optionally the deoxygenation of the solution is completed by addition of an antioxidant.

2. The method for preparing a formulation of claim 1 wherein deoxygenation of the solution is completed by addition of a hydroxypolycarboxylic acid.

3. The method for preparing a formulation of claim 1 wherein the residual oxygen content of the aqueous solution is below 1 ppm.

4. The method for preparing a formulation of claim 1 wherein the residual oxygen content in the aqueous solution is equal to 0.5 ppm or below.

5. The method for preparing a formulation of claim 2 wherein the hydroxypolycarboxylic acid is selected from the group consisting of citric acid, tartaric acid, gluconic acid, saccharic acid, citramalic acid and malic acid.

6. The method for preparing a formulation of claim 2 wherein the hydroxypolycarboxylic acid is an acid or a salt thereof.

7. The method for preparing a formulation of claim 2 wherein the concentration of hydroxypolycarboxylic acid and/or one of its salts is 5 to 200 mg/100 ml of aqueous solution.

8. The method for preparing a formulation of claim 1 wherein the antioxidant is selected from the group consisting of thiols, derivatives of ascorbic acid and reducing sugars.

9. The method for preparing a formulation of claim 1 wherein the antioxidant is ascorbic acid or isoascorbic acid.

10. The method for preparing a formulation of claim 1 wherein the antioxidant is a mixture of cysteine and sodium citrate.

11. The method for preparing a formulation according to claim 1 comprising subjecting

an aqueous solution containing at least one phenolic active principle which is paracetamol, to which an antioxidant and a hydroxypolycarboxylic acid optionally have been added to extreme deoxygenation; introducing

under an inert gas atmosphere, part or all of the deoxygenated aqueous solution into a container previously cleared of the air contained therein; then stoppering

the container under an inert gas atmosphere, to create, in the closed container, a maximum pressure of 65,000 Pa to obtain

an aqueous solution with a phenolic acid principle in a placed closed container, in which the oxygen content is below or equal to 2 ppm.

12. The method of claim 10 wherein the deoxygenation is achieved by bubbling with an inert gas.

13. The method of claim 10, wherein the deoxygenation is achieved by application of vacuum.

14. The method of claim 10 wherein after stoppering, the solution is subjected to sterilization.

15. The method of claim 10 wherein the aqueous solution with an oxidizable active principle is subjected to sterilizing filtration under inert gas.

16. The method of claim 10 wherein the inert gas used for bubbling is nitrogen.

17. The method of claim 10 wherein the inert topping gas is heavier than air.

18. The method of claim 10 wherein the container is cleared of the air contained therein, by insufflation with an inert gas.

19. An injectable aqueous solutions containing, as an active ingredient, a principle of phenolic nature susceptible to oxidation, preserved by the method of claim 1.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,992,218 B2
APPLICATION NO. : 10/332060
DATED : January 31, 2006
INVENTOR(S) : Francois Dietlin and Daniele Fredj

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 12, line 54 in claim 1, "active nature" should read -- active principle of phenolic nature --.

Signed and Sealed this

First Day of September, 2009

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

JS 44 (Rev. 12/12)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. *(SEE INSTRUCTIONS ON NEXT PAGE OF THIS FORM.)*

I. (a) PLAINTIFFS

CADENCE PHARMACEUTICALS, INC.
SCR PHARMATOP

(b) County of Residence of First Listed Plaintiff San Diego, CA
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorneys *(Firm Name, Address, and Telephone Number)*

See attachment hereto

DEFENDANTS

FRESENIUS KABI USA, LLC

County of Residence of First Listed Defendant
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

Attorneys *(If Known)*

'13CV0139 LAB MDD

II. BASIS OF JURISDICTION *(Place an "X" in One Box Only)*

- ❒ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question *(U.S. Government Not a Party)*
- ❒ 2 U.S. Government Defendant
- ❒ 4 Diversity *(Indicate Citizenship of Parties in Item III)*

III. CITIZENSHIP OF PRINCIPAL PARTIES *(Place an "X" in One Box for Plaintiff and One Box for Defendant)*

(For Diversity Cases Only)

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- ❒ 315 Airplane Product Liability
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- ❒ 345 Marine Product Liability
- ❒ 350 Motor Vehicle
- ❒ 355 Motor Vehicle Product Liability
- ❒ 360 Other Personal Injury
- ❒ 362 Personal Injury - Medical Malpractice

PERSONAL INJURY
- ❒ 365 Personal Injury - Product Liability
- ❒ 367 Health Care/ Pharmaceutical Personal Injury Product Liability
- ❒ 368 Asbestos Personal Injury Product Liability

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- ❒ 380 Other Personal Property Damage
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- ❒ 443 Housing/ Accommodations
- ❒ 445 Amer. w/Disabilities - Employment
- ❒ 446 Amer. w/Disabilities - Other
- ❒ 448 Education

PRISONER PETITIONS

Habeas Corpus:
- ❒ 463 Alien Detainee
- ❒ 510 Motions to Vacate Sentence
- ❒ 530 General
- ❒ 535 Death Penalty

Other:
- ❒ 540 Mandamus & Other
- ❒ 550 Civil Rights
- ❒ 555 Prison Condition
- ❒ 560 Civil Detainee - Conditions of Confinement

FORFEITURE/PENALTY
- ❒ 625 Drug Related Seizure of Property 21 USC 881
- ❒ 690 Other

LABOR
- ❒ 710 Fair Labor Standards Act
- ❒ 720 Labor/Management Relations
- ❒ 740 Railway Labor Act
- ❒ 751 Family and Medical Leave Act
- ❒ 790 Other Labor Litigation
- ❒ 791 Employee Retirement Income Security Act

IMMIGRATION
- ❒ 462 Naturalization Application
- ❒ 465 Other Immigration Actions

BANKRUPTCY
- ❒ 422 Appeal 28 USC 158
- ❒ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ❒ 820 Copyrights
- ☒ 830 Patent
- ❒ 840 Trademark

SOCIAL SECURITY
- ❒ 861 HIA (1395ff)
- ❒ 862 Black Lung (923)
- ❒ 863 DIWC/DIWW (405(g))
- ❒ 864 SSID Title XVI
- ❒ 865 RSI (405(g))

FEDERAL TAX SUITS
- ❒ 870 Taxes (U.S. Plaintiff or Defendant)
- ❒ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ❒ 375 False Claims Act
- ❒ 400 State Reapportionment
- ❒ 410 Antitrust
- ❒ 430 Banks and Banking
- ❒ 450 Commerce
- ❒ 460 Deportation
- ❒ 470 Racketeer Influenced and Corrupt Organizations
- ❒ 480 Consumer Credit
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- ❒ 850 Securities/Commodities/ Exchange
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- ❒ 891 Agricultural Acts
- ❒ 893 Environmental Matters
- ❒ 895 Freedom of Information Act
- ❒ 896 Arbitration
- ❒ 899 Administrative Procedure Act/Review or Appeal of Agency Decision
- ❒ 950 Constitutionality of State Statutes

V. ORIGIN *(Place an "X" in One Box Only)*

☒ 1 Original Proceeding ❒ 2 Removed from State Court ❒ 3 Remanded from Appellate Court ❒ 4 Reinstated or Reopened ❒ 5 Transferred from Another District *(specify)* ❒ 6 Multidistrict Litigation

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing ***(Do not cite jurisdictional statutes unless diversity)***:
35 U.S.C. § 100, et seq; 35:145

Brief description of cause:
Civil action for infringement of U.S. Patent No. 6,028,222 and U.S. Patent No. 6,992,218

VII. REQUESTED IN COMPLAINT:

❒ CHECK IF THIS IS A **CLASS ACTION** UNDER RULE 23, F.R.Cv.P.

DEMAND $

CHECK YES only if demanded in complaint:
JURY DEMAND: ❒ Yes ☒ No

VIII. RELATED CASE(S) IF ANY

(See instructions): JUDGE _____ DOCKET NUMBER _____

DATE
01/17/2013

SIGNATURE OF ATTORNEY OF RECORD
s/ Stephen P. Swinton

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RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

CIVIL COVER SHEET
ATTACHMENT

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